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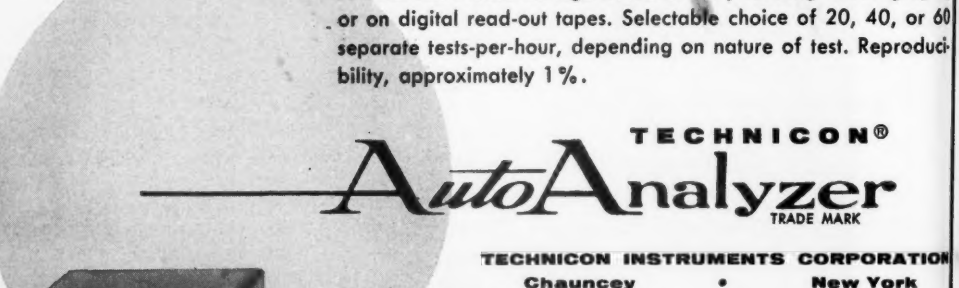

JOINT SESSION OF THE FEDERATION[1]

The Biology of the Cancer Cell

Chairman: ALAN C. BURTON

OPENING REMARKS

F. M. BURNET[2]

From the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

TONIGHT I HAVE THE HONOR and the responsibility of speaking first in a symposium on the biology of the cancer cell. I shall be followed by three speakers, all of whom have made distinguished contributions to the special fields with which they will deal. My position is different. I have made no personal contribution to cancer research and I can claim only three small qualifications for my being here tonight. I like to think that I am a biologist by instinct, just as I am a physician by training, and an experimentalist by a blend of accident and desire.

I can therefore try to introduce this symposium by attempting to look at cancer research, particularly as it involves the laboratory worker, from the two points of view, of the physician with all the human implications of cancer in mind, and of the biologist who is unhappy until he can see any aspect of life with which he is concerned as part of the developing picture of general biology.

Most of my remarks will be concerned with the general biology of cancer. On this occasion, it would be inappropriate to discuss clinical matters but I think it will be evident that neither I, nor anyone else speaking or writing about cancer, can ever quite forget the human aspect.

My personal interest in cancer investigation arose as a by-product of a long-lasting minor interest in the age incidence of infectious disease. In the course of comparing infectious diseases with other types of disease, I came across the well-known relationship by which the mortality from cancer is related to age. If one plots the mortality in each age period against the age both being expressed logarithmically, the points lie very close to a straight line. This log-log relationship holds for total cancer deaths and for most of the individual types which are not strongly influenced by hormonal factors.

I am taking this observation as my starting point because it seems to me that it is crucial to any general interpretation of cancer. From the age of 20 or 30, it appears that we are subject to a random process becoming progressively more evident with age and with an inexorable regularity. The mathematicians agree that the only reasonable interpretation of such a curve is that a process of somatic mutation or some formal equivalent of mutation is involved and that at least two sequential stages are involved. Armitage and Doll have offered two alternatives, the first (1) that a sequence of about six mutational events is needed before overt malignancy appears, the second (2) that two steps only would be adequate provided the clones from the first mutation had a proliferative advantage over normal cells. In this way there would, with age, be a progressively greater population of primary mutant cells within which the second cancer-producing mutation could appear. I can see no reason why intermediate situations with more than two mutational stages and appropriate degrees of proliferative advantage should not also serve equally well and allow some elasticity to cover inevitable variation in biological material.

Probably because of the impression that to adopt such a view of cancer is essentially a defeatist attitude, the somatic mutation theory seems to be quite unpopular in this country. There can be plenty of scope for discussion as to how mutagenic and carcinogenic agents influence cells but there seems to be no possibility of differ-

[1] Philadelphia, Pennsylvania, April 15, 1958.

[2] Dr. Burnet is in the United States as the Flexner Lecturer at Vanderbilt University, Nashville, Tenn.

ence of opinion that the cancer cell, once it has emerged, is a mutant. When we are dealing with non-sexual organisms or cells, a mutation can be defined as an inheritable change affecting cells at random amongst a population and giving rise to a mutant clone whose members can be shown to differ from those descended from unmodified individuals of the original population. On those criteria, cancer cells differ from normal cells by what is formally equivalent to a mutation.

This is not the place to discuss pros and cons of somatic mutation. Instead I shall accept it as the best available concept to bring cancer into relation with general biology. If we examine the implications of the concept, I think we shall begin to see cancer in a new significance—*that it is a process as inevitable as evolutionary progress and of the same general quality.*

When we deal with organisms and species in nature, most mutations are harmful or neutral, and selective survival sees to it that they are eliminated. When, however, an effective new combination of genes eventually appears it will flourish. Even if the new form has only a 5 or 10% survival advantage it will infallibly replace the old over the whole environment for which the advantage holds. This appears to be the standard method by which evolutionary change occurs.

We can look at somatic mutation in rather similar fashion. Mutation is always a process involving the genetic mechanism of a single cell and normally a rare event not to be expected more than once per 10^5 or 10^6 generations. When somatic mutation occurs in the body it is of no significance whatever unless the affected cell gives rise to a descendant clone with a proliferative advantage over its fellows. A cell modified by mutation which either does not replicate or gives descendants without survival advantage over others will be a single unit in the midst of 10^5 or more normal cells in the tissue. No matter how strikingly it may have been modified, it will have no detectable effect. If, however, there is a significant advantage to the mutant clone and it survives the chance of its initial establishment, the proportion of cells of the new type will progressively increase and eventually they may be numerous enough to manifest themselves in one way or another.

It is immaterial whether somatic mutations are due to specifically identifiable mutagens, to the impact of foreign genetic material from a virus or any other source, to excessive hormonal stimulation or to uncontrollable and casual influences, like the normal background of ionizing radiation. The only way in which an observable effect can result is when mutants with a proliferative advantage can emerge. Every significant somatic mutation, whether affecting a normal cell or one that has already mutated, must necessarily be along the road to malignancy. The age incidence of cancer is precisely what would be expected from such a situation. In fact I fancy that the log-log relationship between cancer incidence and age could have been foreseen from the beginning as an inevitable consequence of the evolution of multicellular animals.

This then is one picture—speculative if you like—of how cancer appears in relation to general biology. I should like to spend a few minutes looking at some aspects of cancer in terms of that picture.

Let me first say that I do not consider it is necessarily a defeatist point of view ever in regard to the prevention of cancer. The general pattern of age incidence of any particular type is probably inevitable but some of its parameters are theoretically at least subject to control. Human action can increase or—usually with much greater difficulty—decrease the concentration of mutagenic agents in the environment. A glance at a graph of the lung cancer experience of successive decennial cohorts in the last 50 or 60 years will offer a prototype of the dangers. The lines run parallel but those of each successive cohort are pushed steadily toward the younger ages. (It will be interesting to see whether the popularity of filter tips will push them back!)

We should be able to reduce cancer significantly by the identification of mutagenic agents in the environment and the institution of measures to reduce their impact. In addition the standard approach to remove any causes of chronic irritation or inflammation that might increase turnover of cells in vulnerable tissues is still very much in line.

There is one other clinical aspect of cancer which may justify some comment from this point of view—the use of special procedures to facilitate early diagnosis. In recent years a good deal of skepticism has been expressed as to whether there is in fact any decisive evidence that early surgical treatment improves the proportion of five-year or permanent cures. In a situation where for humane and traditional rea-

sons control groups can never be used, the advantage of early diagnosis may have to continue to be taken on faith. What is certain is that tumors vary in most possible respects and it is, I believe, a general impression amongst pathologists that more help in regard to prognosis is obtainable from how 'malignant' the histology looks than how long the lesion has been present. It would be expected *a priori* that the number of mutational steps and the relative proliferative advantage of the intermediate mutants can vary considerably from case to case. No other type of theoretical approach would seem to be nearly so much in accord with the difficulties that confront the pathologist dealing with precancerous conditions and early malignancy.

Finally, I should like to make a few points in regard to experimental work which seem to be implicit in, or at least suggested by, the biological approach that I have adopted. They will be necessarily brief and without elaboration. There are eight of them.

1) It seems urgent to differentiate—or to prove that differentiation is impossible—between directly mutagenic effects of carcinogens and secondary changes involving increase in cell turnover or providing conditions for the phenotypic emergence of an initiated mutant.

2) Mutational studies on pure clones of mammalian cells along the lines initiated by Puck may become of first-rate importance.

3) Is it possible to demonstrate and assess any effect on large populations of low concentrations of chemical mutagens? In asking this I am influenced very much by current thought about the action of ionizing radiation in inducing leukemia. If there is no threshold in this situation, is it not possible that there is a similar linear relationship of dose and effect with very low concentrations of carcinogens? I once tried to put the present danger of leukemia from global fallout into popular terms by saying that if you equated leukemia with lung cancer, the best estimate I could make was that the risk from current levels was about the same as that from smoking two single cigarettes over thirty years. That statement may be both inaccurate and politically unwise but it does, I think, underline my plea for a look at chemical mutagens from this point of view.

4) There are points of extreme interest that have emerged from the study of viruses in relation to the cancer cell—the existence of Shope's fibroma virus and the way the lesion it produces will melt under the attack of another type of virus for instance—but I cannot see any likelihood or possibility of viruses being shown to be etiological agents in human cancer.

5) In the study of the phenotypic processes by which the mutant cell exercises its proliferative advantage, I believe that much is to be gained by asking what are the positive processes which allow the maintenance of a functioning organ and which of these have been lost when a cancer appears rather than by seeking a *positive* cause for the behavior of a cancer focus.

6) In this field the necessity is to define the controls responsible for tissue integrity. These seem to include what may be called proximity controls dependent on cell surface properties, immunological controls, hormonal controls and perhaps others yet unrecognised.

7) The clonal selection approach would make one rather skeptical of the relevance of much biochemical work on intermediary metabolism of malignant cells as being concerned with a level of organization lower than that in which the significant changes occur.

8) It is possible that continuing study of changes in the biochemical processes that go along with morphological differentiation and regeneration may be more relevant to an understanding of cancer than direct investigation of hypermalignant clones of transmissible tumor cells.

I hope to hear a number of those opinions elaborated or refuted by the speakers to follow.

May I close with some even more general remarks than those I have already made.

We are here as exponents of the experimental approach to biology and I expect that almost every one of us has a divided loyalty. We are at the same time part of what it is simplest to call the cultural pattern of modern science and also members of that larger community which demands that our activities have some relevance to human affairs, in this case to preventive or curative medicine. As scientists we must believe that, provided we work with complete intellectual integrity and in the tradition, as it has developed, of effective experimentation in a particular field, our criterion of value is simply whether the work we do is recognized as adding something significant to human knowledge. As human beings, we are also subject to the hope that what we are doing shall have some bearing on the satisfaction

of human needs and desires. Neither drive is, of course, as simple as I have stated but both are real.

Perhaps in cancer research more than in any other field of experimental biology do we find this divided loyalty. It is not a matter of choosing between alternatives—both are inescapable. Under such circumstances we will always find a wide variety of approaches to the problems of cancer—many of them more frankly empirical than would be found in a field without such deep human implications. This talk is in no sense a protest against this diversity of attack. Its theme is simply that, looked at against the general pattern of life, cancer is a phenomenon of at least as much interest for general biology as for medicine and that perhaps a broader, more biological approach may in the end play a part in teaching us how to prevent and cure what after all is not so much a disease as an intrinsic consequence of the way in which our bodies have evolved.

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THE BIOCHEMICAL APPROACH TO THE CANCER PROBLEM

VAN R. POTTER

From the McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison, Wisconsin

IN A SYMPOSIUM ON CANCER as a broad fundamental problem, a biochemist finds himself in a paradoxical situation: while the other speakers on the program can present acceptable discussions about the problem without mentioning biochemistry, the biochemist cannot discuss the cancer problem intelligently without mentioning biology. And from this point of view, it is only a short step to the conclusion that, indeed, the cancer problem will probably not be understood adequately until the subject can be discussed in one conceptual framework in which the identity of the speaker as biochemist or biologist cannot be learned from the context.

The field of biochemistry is still very young as figure 1 on acid soluble nucleotides may suggest (1). Knowledge of intracellular granules, membranes and compartmentation is only just beginning. The logarithmic phase of discovery of new compounds and new enzymes has been only recently entered and shows no indication of tapering off. It is obvious that we are in great need of general principles to guide us. The only question is, when do we begin to attempt generalization? I believe that in a free society, this problem will take care of itself, as each individual will make his own compromise with uncertainty. For my part, I agree with Dr. Burnet, who believes (2) that "at every stage in scientific development it is necessary to provide the best available generalizations as a guide to effective work, both in the application of knowledge to human needs and in the planning of future research."

In discussing the biochemistry of cancer, it is almost impossible to make a useful generalization that does not tie in with biology, while, as pointed out earlier, it has been perfectly respectable to make biological generalizations that do not tie in with biochemistry. Thus we find that the biologists do not integrate both fields because they feel no need to, and most biochemists in the cancer field do not generalize because of the difficulty in trying to encompass enough of both biochemistry and biology and still do the job adequately. However, the cancer problem has seemed to me to be so monstrous that attempts at generalization or integration of facts are essential, wherever they seem possible as Burnet suggested. I do not believe that this philosophy entails any risk (to science) because for every scientist who generalizes, for example Warburg, there will always be a scientist who presents data with opposing conclusions, for example Weinhouse. Therefore, I seek generalizations knowing that if the ideas are incorrect they will be ignored or disproved and if they are correct they will eventually be found useful.

In the field of cancer, events are moving rapidly toward substantial understanding of the problem. To be more specific, I believe that the following generalizations would be in harmony with the views expressed by Burnet (2) and by Huxley (3) and with contemporary thought in the nucleic acid field (4). They represent my most recent formulation of a general theory of cancer in terms of current thinking and represent a continuation of earlier attempts (5, 6). Criticize, if you will, the generalizations; but please do not regard them as idle speculations. And let the challenges take the form of better generalizations, for it is my opinion that the cancer problem will never be understood until the following points are established in this or in modified form.

1. Genes (DNA) provide molecular patterns for enzymes and surface proteins. The latter may provide the basis for immunological reactions and for organized structures. *a*) This action is mediated in the case of enzymes by the action of enzyme-forming mechanisms involving RNA, but it may be direct in the case of surface proteins.

2. Genes lead to formation of duplicate genes with an inherent error of 1 in 10^5 or 10^6 duplications in organized cells. *a*) Inherent probability of error can be increased by certain chemicals and radiations and is probably decreased in organized cells by a balanced supply of building blocks, since interference with the supply increases mutation rate (7, 8, 9). *b*) Altered genes are duplicated. *c*) Altered genes lead to altered proteins (cf. 10). *d*) Altered proteins make new

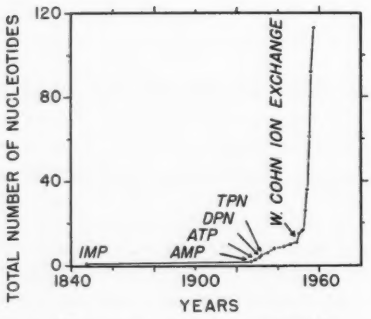

FIG. 1. Discovery of new nucleotides as a function of time. Data from Henderson and LePage (1).

species possible (i.e. gene mutation is the basis of evolutionary adaptation).

3. The possession of gene DNA does not guarantee the presence of the corresponding enzyme (cf. data by Gorini and Maas, 11). *a*) Variable activity of enzyme-forming systems (RNA) mediates between genes and environment. *b*) Activity of enzyme-forming systems is variable because it is modified by presence of inducers or suppressors formed in metabolism or coming from environment. *c*) Action of enzyme-forming systems can be increased or decreased by molecules acting through positive or negative feedback loops that are selected for on the basis of survival value. *d*) Some enzyme-forming systems may not have DNA prototypes. Thus the elements referred to as paragenes by Huxley (3) are probably RNA systems that remain after the mutational loss of the DNA prototype. *e*) The significance of the enzyme-forming systems appears to be that they are the basis of physiological adaptation, i.e. adaptation at the level of the individual organism.

The foregoing 13 points form a body of generalizations that cannot be isolated completely from one another, and current research has to be considered in terms of its effect on the whole body of statements as well as on the individual features. With respect to the cancer problem these conclusions form a sort of beachhead from which further penetrations may be made into the problem. We may now attempt to assess the current status of the cancer problem.

4. Cancer is an evolutionary process along a dead-end street, that is, it is evolution with a known outcome which is the death of the host and of the cancer cell strain, in the absence of therapy, except in rare cases. *a*) I would suggest that normal cells undergo successive (cf. Fisher, 12) somatic mutations (cf. Burnet, 2) that result in the loss of all systems responsible for negative feedback on the specific enzyme-forming systems required for cell division; the latter would seem to include those needed for the synthesis of DNA and the proteins for mitotic mechanisms. In addition, deletion of DNA molecules responsible for tissue specific surface proteins, thereby permitting metastasis and invasion, must be assumed to be obligatory (cf. Burnet, 2), while deletion of catabolic enzymes in general must be considered as cancer-promoting. These three points constitute the most specific theory of cancer that I can formulate at this time; they constitute a biological basis for integrating the current biochemical attack on the cancer problem, as I shall attempt to show. *b*) The successive deletion of the protein-forming systems can theoretically originate only at either the DNA level or the RNA level, although at present there is no need to assume that deletion occurs at only one level to the exclusion of the other. The point is that in a somatic cell we are in no position to judge how soon after the mutation of a DNA molecule we can expect the corresponding enzyme and enzyme-forming system to disappear. If we assume that the deletion occurs at the RNA level, we must assume that at some point in the life of the cell the DNA prototype already had been lost. The important question to us is the biochemical one, namely, can we specify the function of the enzymes whose forming systems (EFS) are lost? Parenthetically, it might be noted that although some cancer cells could theoretically arise by a gain mutation, there is no need to assume that they all do, and no experimental data to support the idea that any do, to my knowledge. Here it may be noted that in a complex organelle with a group of contained enzymes, the loss of one would be a transformation of the organelle (cf. 5) and might be recognized as a gain.

The successive mutations that produce cancer cells may be due *1*) to inherent random errors in nucleic acid replication, i.e. inability to duplicate perfectly, *2*) to errors induced by carcinogens or radiations, or *3*) to loss by segregation of autonomous enzyme-forming systems that fail to replicate fast enough during cell division. The latter situation may result from competition with a viral infection or by combination with carcinogens such as the azodyes (cf. 13). All mechanisms are probably involved in one case or another, and

probably none is uniquely involved in all types of cancer. There seems to be no logical necessity for trying to fit all cancer phenomena into the virus hypothesis unless the definition of a virus is broadened to include any nucleoprotein, endogenous or exogenous, whether it has natural vectors of transmission or not. However, I think most people might agree that it is more appropriate to begin thinking in terms of nucleoprotein behavior per se rather than to attempt to make all nucleoproteins fit an expanding definition of a virus. *c*) The evolutionary process does not end with the formation of cancer cells, but continues, leading to the formation of drug resistant strains (cf. Law, 14). Similarly, cancers of low malignancy evolve into cancers of increasing malignancy. Here I am referring to the phenomenon of progression. *d*) "In most cases each individual (spontaneous) tumor is the equivalent of a biological species so that the number of species is the same as the number of individuals" (Huxley, p. 476, ref. 3). *e*) The problem in cancer chemotherapy is to recognize the emergence of selected mutants and to change the therapy as quickly as selection occurs, or to use combination therapy. *f*) The virus theory seems inadequate to explain all aspects of cancer heterogeneity.

The foregoing generalizations represent a minimum collection representing what is meant by an integration of biological and biochemical concepts of cancer. They are obviously not the final word. Moreover, they fail to integrate the immunological and histocompatibility data with the metabolic data. Finally, the biochemical feedback loops need to be specified in detail and these have to be coordinated with host-tumor interaction. But the work on these details is well underway and will be discussed below. It is my conviction that these concepts have progressed too far to be set aside: they can be modified and extended but they can never be rejected as irrelevant. They represent an integration of the cancer problem with the basic concepts of nucleic acid function and of evolution.

With these generalizations in mind, we must now try to expand the biochemical particulars of the story, and we will begin with a brief historical account.

HISTORICAL BACKGROUND

The outstanding name in the field of cancer biochemistry is that of Warburg, but his numerous other contributions attest the fact that he has not regarded cancer as his chief responsibility. Indeed, although the 'Warburg theory' of cancer is frequently referred to, Warburg himself has never claimed that his views on the origin of cancer constituted a general theory of cancer, and at the time his views were announced (1924–1930) it would have been impossible to foresee the subsequent events that have made a general theory possible.

However as recently as 1956 Warburg stated that "the problem of cancer is not to explain life but to discover the differences between cancer cells and normal growing cells. Fortunately this can be done without knowing what life really is" (15). It is also clear that Burk has taken a similar position (16). On the contrary, I feel compelled to say that we can understand cancer only to the extent that we understand life, and that this should not be a cause for pessimism, since cancer is clearly a much simpler problem than many aspects of life, such as embryogenesis and differentiation, for example.

Warburg believed in 1930 that the shifting of the energy production from the aerobic to the anaerobic state was the cause of cancer and continued to hold this view in 1956 (15), when he emphasized the concept of balance, suggesting that the important point was the ratio between the absolute values for glycolysis and for respiration. The idea is that glycolysis tends to be increased and respiration tends to be decreased in such a way that when both are occurring simultaneously the net rate of glycolysis will always exceed the oxygen consumption. Indeed, this simultaneous measurement is the basis of the manometric test daringly proposed by Burk and Schade (16) who agree with Warburg's conclusions. Since only one clear-cut exception to their

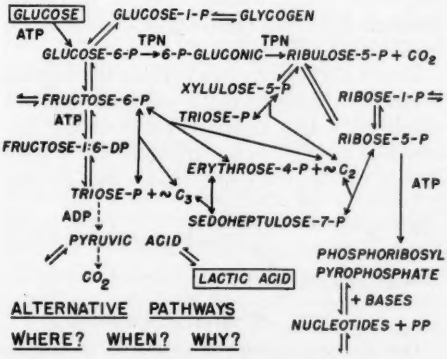

FIG. 2. Alternative pathways of glucose metabolism, adapted from Horecker and Mehler (22).

generalization would seriously damage its validity it is worth noting that none have been published, to my knowledge.

The views of Warburg and Burk have been rather categorically denied by Weinhouse (17), who accepts the idea of a high glycolysis but believes that it occurs "despite quantitatively normal occurrence of carbon and electron transport." Too many words have already been expended on this subject without any real insight into what should be compared and what constitutes a "normal occurrence of carbon and electron transport." As emphasized earlier (6, 18, 19), every normal tissue is characterized by a unique balance between the various enzymes involved in metabolism, and whenever tumor tissues are studied extensively enough (14) it is found that they too differ from each other in the balance between the various enzymes that are studied. In general, the cancer tissues are at the low end of the spectrum in terms of a number of respiratory enzymes (18, 19), and quite recently we found that in several cancer tissues two enzymes, transhydrogenase and TPN-cytochrome *c* reductase, representing alternative paths of reaction between reduced triphosphopyridine nucleotide and cytochrome *c*, were either absent or present at extremely low levels. Talalay and Williams-Ashman (20) recently pointed out that a steroid hormone estradiol together with its dehydrogenase, which operates with either DPN or TPN, functions as a transhydrogenase and noted the possible relation of this function to growth. It is clear that more studies on alternative hydrogen transport mechanisms need to be made and integrated with the metabolism of growth (19) before concluding that the last word has been said in the Warburg-Weinhouse debate. Similar views on alternative pathways have been expressed in a recent review by Kit and Griffin (21).

Here it might be emphasized that the essential nature of the cancer problem will never be solved simply by making measurements of oxygen consumption or CO_2 output. Glycolysis and respiration do not occur in compartments that are connected to the rest of the cell by a single pipe labeled ATP. In the glycolytic and pentose cycles, for example, many of the intermediary metabolites face multiple alternative pathways as shown in figure 2 (cf. 22). "Since a given compound may react along several alternative pathways, each of which passes through a different activated state and each of which is catalyzed by a different enzyme, it is apparent that the balance between the several enzymes actually determines the course of metabolism. This amounts to much more than a mere hastening the attainment of equilibrium" (6, p. 19). The acceptance and understanding of the role of alternative metabolic pathways is fundamental to any attempt to develop a general theory of cancer, because the existence of alternative metabolic pathways is what makes the loss of any given enzyme significant.

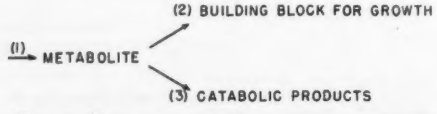

FIG. 3. Basic concept of cancer as an enzyme deletion (6). Loss of a catabolic enzyme on pathway *3* is assumed to stimulate competitive pathway *2*.

The basic concept for the enzyme deletion hypothesis of cancer metabolism is illustrated diagrammatically in figure 3. The essence of it is that a loss of enzymes along catabolic pathways *3* is postulated to occur, thereby stimulating synthetic pathway *2* (6). At the time this simple idea was proposed nothing was known about enzyme forming systems and the phenomenon of negative feedback. With these more sophisticated insights into cell adaptation mechanisms we can understand that the loss of pathway *3* may not only stimulate pathway *2* by providing less competition, but it may actually increase the amount of enzyme production for pathway *1* or *2* by feedback mechanisms.

At this point it may be pointed out that the deletion hypothesis in one form or another is being given consideration in biological terms, for example by Burnet (2) as well as in general metabolic terms, for example, by Haddow (23). These investigators have been strongly influenced by the work of the Millers (13), who showed that in the production of liver tumors, the carcinogenic azo-dye combined with certain liver proteins while no such combination could be found in the tumors. The Millers (13) have also discussed the general metabolic requirements of such a mechanism.

The problem now facing cancer investigators is whether evidence as to the exact nature of the protein or proteins thought to be deleted can be specified.

It is clear that Burnet, as a biologist, is impressed with the immunological hypothesis of H. N. Green which holds that the protein lost is a

tissue specific 'marker' protein which in addition would have to be "one of the points necessary for the organisms control" (2). It is obvious that if the theory of successive deletions is correct, both metabolic and immunologically specific functions might be lost. Thus regardless of whether we are discussing an immunological theory or a virus theory or any other biological concept, in the end the cancer cell or normal cell divides or fails to divide in accordance with the enzymes that it contains, the way in which they are spatially segregated, and the physical and chemical factors that surround it. Since cell division appears to be closely related to DNA synthesis I believe it is worthwhile to consider some of the available evidence on alternative pathways in relation to DNA synthesis.

If we look for enzyme deletions in cancer cells the first question that must be answered is whether or not we have an appropriate normal cell for comparison (18, 24). Recently a number of enzyme assays have been carried out on the Novikoff hepatoma, which is probably though not certainly derived from parenchymal liver cells (25). Since the number of tumor strains is now very large and the findings frequently divergent, it would be helpful if investigators could investigate a few selected types rather intensively. A beginning in this direction has been made with the Novikoff hepatoma (25). It is fortunate that a number of studies involving alternative metabolic pathways have been carried out with liver and with hepatoma though not all studies cited have been carried out with the Novikoff hepatoma. The concept of alternative pathways applies especially well to a compound such as uracil (fig. 4). Rutman, Paschkiss and Cantarow (26) showed that uracil is poorly used for nucleic acid synthesis in liver because its degradation is so active in this tissue, while Canellakis showed

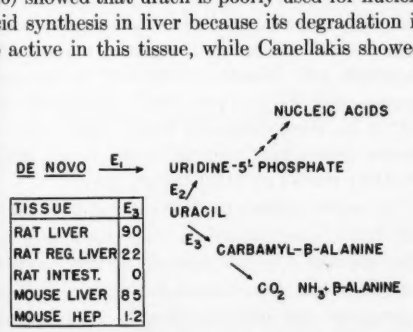

FIG. 4. Alternative pathways open to uracil. Pathway *3* is weak in hepatoma and intestine but strong in liver (27). Data as per cent conversion to $C^{14}O_2$.

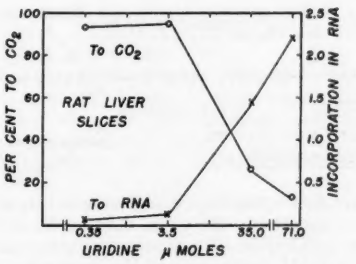

FIG. 5. Incorporation of uridine-2-C^{14} into RNA of liver slices when concentration exceeds capacity of degradative enzyme system. Based on data from Canellakis (27). Incorporation into RNA expressed as per cent replacement of uridylic acid.

that only when the degradation system is saturated can uridine be incorporated into liver RNA (27); see figure 5. However the degradation system is weak in hepatoma and the compound is readily utilized for nucleic acid synthesis (26, 27). This situation in liver and in hepatoma represents a model system for chemotherapy under the deletion hypothesis and in fact led to the synthesis of 5-fluorouracil by Heidelberger and collaborators (28). If one of the enzymes deleted from the tumor is an enzyme that normally prevents the utilization of a given metabolite such as uracil by destroying it, the corresponding antimetabolite (fluorouracil) should be less toxic to the normal tissue because of its destruction and more damaging to the tumor because it is not degraded there. In the instance cited, the catabolic enzyme is also weak in intestinal tissue, but, despite this fact, differential inhibition of tumor tissues was achieved by Heidelberger and his collaborators (29), who have shown, in fact, that 5-fluorouracil is not catabolized by tumor cells.

Model systems of negative feedback in which EFS systems have been suppressed by metabolic products in a seemingly purposeful (that is, selected) manner have been shown in several instances in bacteria. Yates and Pardee (30) have shown how uracil can suppress the *de novo* synthesis of uridylic acid from aspartic acid in *E. coli* (fig. 6). Gorini and Maas (11) showed how the presence of arginine could completely suppress the formation of its own synthesis in an *E. coli* strain. A feedback situation similar to that studied by Yates and Pardee has been observed in a child (Dr. J. A. Bain, personal communication).

It seems likely that various enzymes in normal tissues are maintained at given levels by the

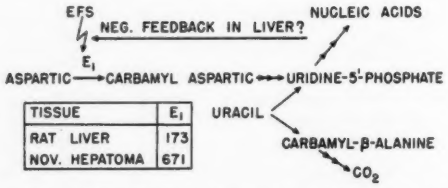

FIG. 6. Feedback mechanism regulating pyrimidine biosynthesis. Based on data on *E. coli* from Yates and Pardee (30). Aspartic transcarbamylase assays from Auerbach and Waisman (33). Units in μM/gm dry wt/hr.

regulation of the corresponding enzyme forming systems, and that certain enzymes in hepatoma might be increased by a lowering of the level of negative feedback on enzyme synthesis. Thus Calva, Lowenstein and Cohen (31) and Calva (32) found increased levels of aspartic transcarbamylase in regenerating liver and in various tumors, while Auerbach and Waisman (33) found approximately four times as much of this enzyme in the Novikoff hepatoma as in normal liver. From the work of Yates and Pardee (30) with *E. coli* it might be inferred that the hepatoma contains less of the metabolite that normally suppresses the EFS system for aspartic transcarbamylase. Since Canellakis found an apparent absolute increase in uracil conversion to RNA in regenerating liver and hepatoma (27), it might be supposed that in normal liver this process may be suppressed by a product of uracil catabolism while similar mechanisms can be visualized for pathways leading to DNA (24). Current studies are being directed toward this problem in terms of thymidine metabolism (34). The important point is that normal adult tissues have the problem of not growing even in the presence of both *de novo* and preformed sources of building blocks. One of the ways in which this might be done would be to suppress the synthesis of a rate limiting enzyme between uridylic acid and thymidine triphosphate. This might be done by means of a metabolite derived from some intermediary metabolite whose presence provided relevant information, such as thymidine (34). We should also consider other possible control points in the regulation of DNA synthesis and mitosis and consider the possibility of feedback mechanisms involving tissue specific protein molecules other than the more obvious metabolites.[1]

[1] A discussion of hormonal feedback on enzyme forming systems has been presented elsewhere (Potter, 39).

TABLE 1. CATABOLIC ENZYMES REPORTED TO BE LOW OR MISSING IN THE NOVIKOFF HEPATOMA*

Enzyme	Reference
Glucose-6-phosphatase	Weber and Cantero (35)
Xanthine oxidase	deLamirande and Allard (36)
Uricase	Novikoff (25)
Esterase	Novikoff (25)
Glutamic dehydrogenase	Allard, *et al.* (37)
Transhydrogenase	Reynafarje and Potter (38)
TPN cytochrome *c* reductase	Reynafarje and Potter (38)
Tryptophane peroxidase†	Auerbach and Waisman (33)
Tyrosine transaminase†	Auerbach and Waisman (33)
Threonine dehydrase†	Auerbach and Waisman (33)
Phenylalanine hydroxylase	Auerbach and Waisman (33)
Cysteine desulfurase	Auerbach and Waisman (33)
p-OH phenylpyruvic acid oxidase	Auerbach and Waisman (33)
Arginase	Auerbach and Waisman (33)

* For data on other tumors cf. Greenstein (18).
† The enzyme-forming systems also appeared to be missing (33).

It is important to note that there are now a number of catabolic enzymes that are missing or very low in the Novikoff hepatoma (table 1). These include glucose-6-phosphatase (35), xanthine oxidase (36), uricase (36), glutamic dehydrogenase (37) which have been studied by the Montreal group, and tryptophane peroxidase, tyrosine transaminase, threonine dehydrase, phenylalanine transaminase, phenylalanine hydroxylase, cysteine desulfurase, p-hydroxyphenylpyruvic acid oxidase and arginase, reported by Auerbach and Waisman (33) and transhydrogenase, and TPN-cytochrome *c* reductase reported by Reynafarje and Potter (38). Some of these enzymes were reported to be low or missing in earlier studies on other tumors (18).

The recent studies by Auerbach and Waisman (33) have demonstrated in some cases that not only are the enzymes missing in the Novikoff hepatoma, but the corresponding enzyme-forming systems are also not demonstrable. These include tryptophane peroxidase, tyrosine transaminase and threonine dehydrase.

In conclusion it should be said that in emphasizing deletions of catabolic enzymes (by deletion

of RNA or DNA templates) and their possible relation to the persistent hyperplasia of cancer tissue, we do not imply that there may not be deletions of important tissue specific surface proteins also. Indeed, we are assuming that such deletions occur. The available evidence would merely suggest that if important surface proteins are lost, these losses must occur concomittantly with metabolic effects, and we have here attempted to show how several current studies provide data to support the concept of how the process of cell division might be enhanced in several ways by the loss of appropriate catabolic enzymes. The available evidence places the enzyme forming systems in a key position, controlled from above by the DNA pattern, and controlled from below by the molecules in the metabolic pool. Further studies on these three inter-related levels of cell organization will certainly increase our understanding of the cancer problem, but in addition they will increase our ability to cope with other diseases and indeed the whole problem of man's adaptation to his environment, his control of his environment and, possibly, control of himself.

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THE RADIOBIOLOGY OF THE CANCER CELL

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WITHIN ONLY A FEW MONTHS after its discovery in 1895, the x-ray was employed empirically to treat superficial cancers, with encouraging results (1). So rapid was its subsequent introduction into tumor therapy that by 1909 radiation had been used to treat more than 3000 patients with malignancies of nearly all types (2). Along with early recognition of the usefulness of the x-ray in the treatment and detection of neoplasms, however, its carcinogenic action on the skin (3) and hemopoietic system (4) were noted.

In the half century that has elapsed since these initial observations, ionizing radiations have come to play a major role in the study of cancer. Efforts to improve the radiotherapy of tumors have led to systematic study of the effects of radiation on neoplastic and on normal cells, from which has come knowledge of the fine structure, reproduction, growth, metabolism and genetics of the cell. At the same time, a wealth of information has been obtained about the mechanism of carcinogenesis through experiments with radiation-induced neoplasia.

Understanding of the biologic action of ionizing radiation, in tumorigenesis and in tumor therapy, requires knowledge of the nature of the changes caused by the interaction of radiation with the living cell. The sequence of events initiated by the absorption of radiation is as yet poorly known, but advances in the radiobiology of cancer will depend henceforth largely on elucidation of radiation effects at the atomic and molecular levels, and of the influence of these effects in determining changes in the function and structure of cells.

NATURE OF EFFECTS OF RADIATION ON THE CELL

Primary Physicochemical Effects. The biological action of ionizing radiation is ascribed to chemical changes resulting from radiation-induced excitation or ionization of atoms in the cell (5). As each ionizing photon or particle is absorbed in passing through matter, it produces ion pairs along its path at distances from one another that vary with the energy, mass and charge of the radiation (fig. 1).

Although this process has been reasonably well characterized in simple gases, relatively little is known as yet about the reactions produced by radiation in complex solutions such as exist in living cells. It is clear, however, that alteration of a biologically important molecule may occur not only by the collision of an impinging particle itself, but also through reaction with radicals (H_2O_2, HO_2, OH radicals, H atoms, organic peroxides, activated water) formed by interaction between the radiation and atoms and molecules in the surrounding solvent (6). It is significant that in mammalian cells drastic effects are caused by a single ion per 10^2 to 10^6 molecules (7) suggesting inactivation of key cellular constituents, such as nucleoproteins or enzymes.

Biochemical Effects of Irradiation. Although the intermediary chemical reactions resulting from ionization can only be postulated as yet, a wide variety of biochemical changes has been observed in irradiated cells (8, 9). Of these, perhaps the most important is inhibition of deoxyribonucleic acid (DNA) formation, which has been studied extensively since the pioneer work of Euler and Hevesy (10) and Mitchell (11). Studies with isotopes indicate that DNA turnover may be inhibited in certain tissues by doses as low as 100 r (12–14), but since DNA synthesis is normally related to cell division and since even smaller doses of radiation inhibit mitosis (14), it is not clear whether radiation depresses DNA formation directly or through mitotic inhibition. That DNA synthesis may occur, however, in the presence of mitotic inhibition has been observed by Gaulden (14) and by Holmes (15). The latter noted that irradiation shortly after partial hepatectomy depressed mitosis in the regenerating rat liver but failed to stop production of DNA after it had already begun. Similar results have been obtained with bone marrow by Lajtha *et al.* (16). The mechanism of the depression is not

[1] Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

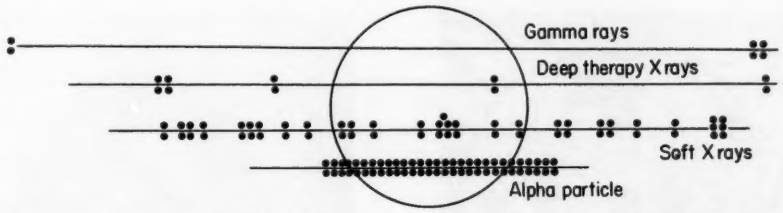

FIG. 1. Separation of ion pairs in relation to the size of a virus particle 27 mμ in diameter (L. H. Gray, *Brit. Med. Bull.* 4: 11, 1946).

clear, but the available evidence suggests that interference with DNA formation is a general block rather than an inhibition of any particular step in synthesis (17).

The effect of radiation on DNA turnover in tumors of various types has been observed to vary in proportion to the amount of cytologic injury produced (15, 18–21). DNA synthesis may be inhibited, however, before there is cytologic evidence of cell death (19).

Although variable in degree, the inhibitory action of radiation on ribonucleic acid (RNA) formation appears to be much less pronounced than effects on DNA formation (15).

Oxidation of sulfhydryl-containing enzymes has also been regarded as an important mechanism of radiation injury (22); however, the amounts of radiation required to affect enzymes *in vitro* are large in comparison with the doses that kill mammalian cells. Furthermore, a given enzyme may respond differently in different tissues, depending on the conditions of the experiment (9). Inhibition of oxidative phosphorylation and of glycolysis has been noted in a number of mammalian tissues irradiated *in vivo* (9, 23), but as yet it cannot be decided whether these changes are primary effects of irradiation or secondary to injury of other systems in the cell (24).

In short, although nongenetic types of damage have been noted (25), it appears probable that the primary mechanisms of injury result from chromosomal or genetic changes (26).

Chromosomal and Genetic Effects. The most radiosensitive biological response known is the gene mutation, the induction of which varies linearly with dose, irrespective of dose rate (27). From the relation between mutation yield and dose it is inferred that production of a gene mutation requires but a single ionization of the gene (5). Perhaps equally sensitive is the induction of lysogenicity in bacteria, which may likewise result from one ion or radical (28).

A single ionizing particle (but probably more than one ion) may also cause a change in the structure of the chromosome, which is visible microscopically as a break in the chromosomal thread (fig. 2). The broken ends of the chromosome usually rejoin, restituting the original structure; however, reunion of the ends may not take place, or union may occur with broken ends of other chromosomes, giving rise to various types of chromosomal deletions and rearrangements (fig. 3). Since chromosomal interchanges require the effectively simultaneous occurrence of breaks in two or more chromosomes, they are seldom produced by a single ionizing particle of low linear ion density, such as the x-ray; hence these changes are referred to as 'multihit' aberrations. The yield of such effects is dependent on the radiation intensity in the case of x-rays and gamma rays but independent of the radiation intensity in the case of heavy particles (29, 30). Another type of chromosomal change known as 'stickiness' is the tendency for affected chromosomes to adhere to one another during mitosis, resulting in clumping at metaphase and bridge formation at anaphase (fig. 4). The prominence of the resulting nuclear abnormalities in irradiated cells has been stressed repeatedly by morphologists since the turn of the century (31). Loss of Feulgen-staining DNA, with intranuclear vacuolation (32), and 'paling' of chromosomes (33) are other visible radiation-induced changes of nucleoprotein that have been described.

Although the nature of the chromosome break and the mutation cannot yet be defined in precise biochemical terms, it is inferred that these changes result from some type of chemical alteration in nucleoprotein. Since broken chromosomes may restitute and since in certain instances back mutations may occur, it would appear that the underlying changes are not necessarily irreversible. The chemical effects of radiation on DNA *in vitro* have been observed to include breakage of hydrogen bonding between the threads, deam-

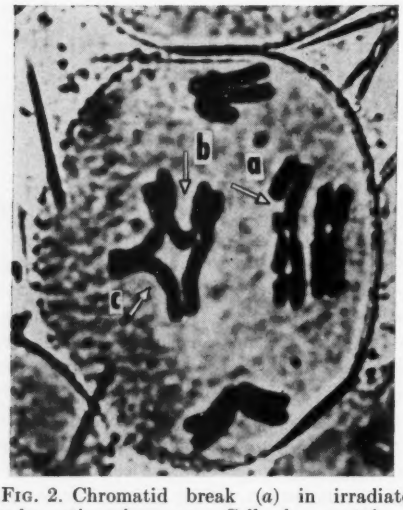

FIG. 2. Chromatid break (*a*) in irradiated *Tradescantia* microspore. Cell also contains a chromatid interchange [dicentric chromatid (*b*) with acentric fragment (*c*)]. Acetocarmine; ×1220 (courtesy of H. E. Luippold).

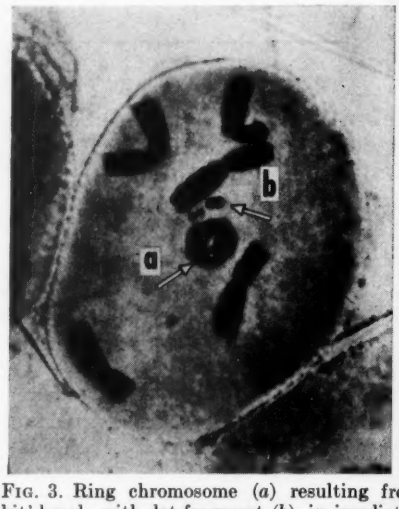

FIG. 3. Ring chromosome (*a*) resulting from '2-hit' break, with dot fragment (*b*), in irradiated *Tradescantia* microspore. Acetocarmine; ×1220 (courtesy of H. E. Luippold).

ination of the bases, dehydroxylation, fission of the sugar-base linkage, oxidation of the sugar and breakage of the nucleotide chains with liberation of inorganic phosphate (34). The relation between chemical changes of DNA *in vitro* and genetic lesions *in vivo* is, however, conjectural. It is noteworthy that the former apparently require substantially larger amounts of radiation than the latter. Furthermore, there is evidence that nucleoprotein itself is more radiosensitive than either of its component parts, DNA and protein, and that its viscosity (fig. 5) and colloidal properties may be affected by relatively low doses of radiation (35, 36). In the alteration of nucleoprotein *in vivo*, an important role may conceivably be played by proteolytic and nucleic acid-splitting enzymes that are activated by irradiation (36–38).

Major deviations from normal chromosomal balance are usually incompatible with proliferation of a cell or its progeny, as are certain point mutations; in some somatic cells, however, only a fraction of the genome may be necessary for survival and differentiation. Minor changes, though nonlethal, may impair the viability or function of the cell or may have no detectable effect (27).

EFFECTS OF RADIATION ON GROWTH AND SURVIVAL OF CELLS

Effects on Survival. Irradiated cells may degenerate and die during or shortly after exposure without entering mitosis, may survive in a resting phase until they begin to divide, or may give rise to cells that degenerate after completing several outwardly normal division cycles (39). Four such types of injury of varying degrees of radiosensitivity have been characterized by Puck and Marcus (40) in the isolated HeLa cell irradiated *in vitro: 1*) a cell injured by x-rays in the dose range below 600 r often retains the ability to divide for one to five generations but is unable to reproduce itself indefinitely (i.e., from a colony of more than 50 normal cells). Judged by this criterion, the 'survival' of HeLa cells declines exponentially with dose, the mean lethal dose being 96 r (fig. 6). (Similar dose-response curves have also been obtained for human cells of non-neoplastic origin (41).) *2*) HeLa cells surviving doses below 600 r show slowing of growth, or of colony formation. *3*) Those exposed to doses above 600 rarely divide even once but may enlarge to gigantic size. *4*) After still larger doses, the yield of enlarged cells drops, indicating prompt cell death, but even after 10,000 r, 5 to 10% of the original inoculum survive for a time as giant cells.

These observations are consistent with the effects of radiation on normal and malignant cells *in vivo*. Since it can be calculated from figure 6 that a dose of 500 r would kill 99% of cells with with the radiosensitivity of HeLa cells, the marked depletion of germinal cells in neoplasms

and in the bone marrow, lymphoid organs, gonads and intestinal crypts of most mammals exposed to 500 r suggests that these cells are of the same order of radiosensitivity as HeLa cells. For certain types of spermatogonia, the median lethal dose has actually been demonstrated to be 20–25 r (42), and the sensitivity of ascites tumor cells irradiated *in vitro* is also nearly as high, if judged on the basis of chromosomal aberrations (43), as is that of normal human kidney cells (44). Furthermore, by extrapolation of the dose-response curve for HeLa cells, it may be estimated that destruction of all members of a large population comprising many billions of such cells (e.g., a tumor) would require a dose of several thousand roentgens, which is in agreement with clinical (45) and experimental (46) observations on the radiocurability of tumors. It also follows from this that the radiocurability of a given type of tumor varies inversely with the number of cells it contains, or with its size (47), which is logical on the basis of the distribution of ions in relation to the total dose absorbed in tissue (48).

Giant cells of the type formed by injured HeLa cells have been noted repeatedly in irradiated tissues (49) and have been viewed clinically as a criterion of tumor radioresponsiveness (50). It is noteworthy that a similar type of cellular enlargement has been noted in bacteria after irradiation (5) and after interference with thymine synthesis by chemical means (51). Hence, the effect may be attributed to persistence of part of the cell's synthetic machinery after loss of the ability to divide. Possibly related to this finding is the observation, disputed by some observers (52), that normal and neoplastic cells rendered incapable of dividing by irradiation may retain the capacity to undergo differentiation, a process thought to favor tumor regression (53).

The ability of irradiated cells to survive until entering mitosis or even until after completion of several mitotic divisions helps to explain the lag that usually separates irradiation and the earliest outward appearance of injury and suggests an explanation for the relative radiosensitivity of rapidly dividing cells in contrast to the relative radioresistance of cells that do not divide. The postponement of death until mitosis also supports the view that radiation injury affects primarily the reproductive apparatus of the cell (5).

Mechanisms other than genetic or chromosomal injuries have, however, been postulated to account for death, especially death occurring before cell division. This type of degeneration, commonly encountered after large doses of radiation and after particulate radiations (54, 55), is unexplained as yet (5). Under many conditions, the proportion of cells exhibiting chromosomal aberrations is small in relation to the total number dying (56).

Effects of Mitosis. Minute doses of radiation delay the onset of mitosis or may cause cells already in early prophase to revert to a resting stage (39). On the other hand, cells irradiated late in prophase or in subsequent stages of mitosis generally continue to divide, although their rate of division may be altered. These effects cause reduction in the proportion of dividing cells in any given population, the reduction varying in degree and duration with the dose. When mitosis is resumed, the proportion of cells dividing may temporarily exceed or 'overshoot' normal (fig. 7), owing presumably to synchronous division of cells accumulating in late interphase during the period of radiation-induced mitotic inhibition. Despite extensive study of the effects of radiation on mitosis, the cause of mitotic inhibition is not yet known. In some systems cell division may be delayed for several successive cell generations (57). Though the use of radiation microbeams, by which the effects of localized irradiation of the spindle, the centriole, individual chromosomes and other organelles is being investigated (33, 39), our knowledge of the normal mechanisms of mitosis and our understanding of the effects of radiation on cell division should be greatly advanced.

FACTORS INFLUENCING THE RADIATION RESPONSE

Radiosensitivity. Relatively high radiosensitivity, a trait characteristic of rapidly dividing cells, constitutes the property of cancer cells that enables their selective destruction by irradiation. The radiosensitivity of neoplasms varies widely, some tumors being relatively radioresistant (46). Furthermore, the response of a given type of tumor may vary from patient to patient or from one region to another in the same patient (58). Although the radiocurability of a tumor is not necessarily dependent on its radiosensitivity, radiobiologists have long sought to understand the mechanism of variations in radiosensitivity and to influence them at will. The following are some of the factors affecting radiosensitivity that have been studied thus far.

Perhaps the most important determinant of radiosensitivity is position on the *phylogenetic*

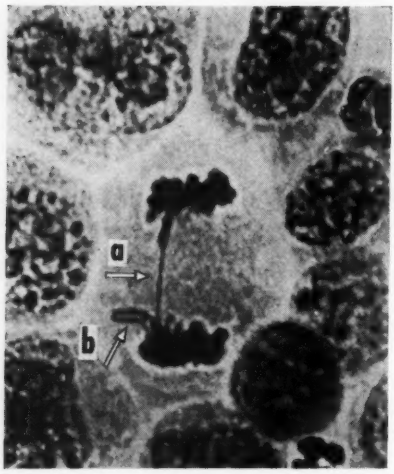

FIG. 4. Irradiated mouse Ehrlich ascites tumor cell in anaphase, showing a chromosome bridge (*a*) and associated fragment (*b*). Acetocarmine; ×1220 (courtesy of Alan D. Conger).

scale. For example, the lethal dose for microorganisms exceeds 10^3 r and in some instances even 10^5 r (59) in contrast to the lethal dose of 10^2 r, or less, for mammalian cells. It is logical to attribute the greater vulnerability of mammalian cells to their greater complexity or to a larger size of the genetic target, but this explanation is yet to be defined in terms of specific genetic or biochemical mechanisms.

Within a given family of cells, radiosensitivity is greatest in the haploid state and decreases with higher degrees of *ploidy* (fig. 8). The exponential relation between survival and radiation dose characteristic of haploid cells may be explained either on the basis that killing results from a single hit in a sensitive region of the cell or that cells in a population are distributed exponentially with respect to radiosensitivity, existing evidence favoring the former hypothesis (5). In contrast to the simple exponential response of haploid cells, the sigmoid survival curves characteristic of polyploid cells are more complicated. These, however, can be satisfactorily explained, in general, on a single-hit per unit, multiunit basis, according to the formula

$$S = [1 - (1 - e^{-kD})^n]^m$$

in which S is the fraction of the population surviving, D the absorbed dose of radiation, n the number of units per cell that must each be hit at least once to cause death, m the number of sets of such units per cell, and k a constant, the value of which varies with the radiosensitivity of the hit process, not all hit processes within a given cell being necessarily of the same radiosensitivity (60). If this formula is applied to survival data for cells with varying numbers of nuclei and varying ploidy, n is characteristically 1 for haploids, 2 for diploid, 4 for tetraploid cells, etc. (61, 62), and m is 1 for uninucleate, 2 for binucleate, 3 for trinucleate cells, etc. (60). Although certain discrepancies remain to be explained (41, 60, 63), a combination of recessive and dominant lethal killing may account for the observed results (64). This interpretation of survival curves, with allowance for the production of hits by radiation-induced radicals as well as by radiations themselves, constitutes perhaps the most compelling argument in favor of genetic or chromosomal mechanisms as the primary cause of cell death. Analyzed in this manner the dose-response curve for survival of HeLa cells (fig. 6) is a typical 'two-hit' curve, suggesting that killing requires simultaneous injury of two units per cell, presumably chromosomal units (40). This, of course, is to be expected of most mammalian cells, since they are diploid; however, in the HeLa cells, which may have been aneuploid or polyploid because of prolonged culture, the significance of the 'two-hit' response is uncertain. For cancer cells in general, relatively high radiosensitivity is probably not attributable to reduced ploidy or low 'hit number.' On the contrary, the frequent spontaneous emergence of *hyper*diploid variants among cancer cells (65, 66) constitutes a theoretical mechanism for development of radioresistance (67).

The radiosensitivity of a cell is also influenced by the *stage in the division cycle* at which it is irradiated, for reasons as yet largely unknown. The stage of greatest sensitivity varies with the effect observed and with the type of cell studied (67, 68). Sensitivity to chromosomal damage is maximal in prophase or metaphase for most types of cells (67). Susceptibility to mitotic inhibition, on the other hand, is greatest in early prophase or late interphase (39). Maximal interference with DNA synthesis probably requires irradiation preceding or in early interphase, in view of the observations that DNA formation normally occurs from late telophase through early prophase (14) and that once DNA production has started it is no longer so easily curtailed by irradiation (15, 16).

The enhancement of radiosensitivity by *oxygen* has been studied extensively since Holthusen's observation (69) that cells are rendered relatively

radioresistant by anoxia. This action of oxygen has been ascribed largely to its radiochemical effects, i.e., to formation of oxidizing radicals and peroxides (70). Other effects, however, have been postulated (71, 72), and all systems are apparently not sensitized by oxygen (71). The sensitizing effect of oxygen on tumor cells (73), as on other types of cells, is greater with x-rays than with neutrons and other densely ionizing radiations, as might be anticipated on radiochemical grounds. Not only does oxygen influence the amount of initial injury per unit dose, but it may also affect repair; in plant cells, at least, the restitution of broken chromosomes requires energy which is obtained through oxidative pathways and hence is oxygen dependent (74).

The influence of *temperature* on radiosensitivity varies according to the time during which the cells are treated (before, during or after irradiation), with the range of temperature investigated, and with the biological material studied (71). In general, radiosensitivity is diminished in cells irradiated at subzero temperatures, presumably because of reduced formation and diffusion of radicals. Mammalian tissues irradiated at or slightly above 0°C may exhibit reduced (75–79) or enhanced (80) radiosensitivity, depending on the oxygen tension and other factors. Chilling after exposure retards the appearance of radiation injury (71) and may in certain instances promote recovery (81, 82).

Some of the modifications of radiation injury caused by variation in oxygen and in temperature indicate the importance of *metabolic factors* in radiosensitivity. Various alterations of cellular metabolism have been observed to affect the response to irradiation, but the mechanisms of these effects are largely unknown (71, 83). Although in many instances they involve changes in oxygen tension or mitotic rate, other factors also seem to be important. Moreover, the high radiosensitivity of rapidly dividing cells may conceivably depend less on the association between mitosis and cell death than on metabolic factors. This is suggested by discrepancies between radiosensitivity and mitotic rate; e.g., the greater radiosensitivity of slowly growing basal cell carcinomas than that of more rapidly growing squamous cell carcinomas (45); and the conspicuously high radiosensitivity of mature, nondividing lymphocytes (84). The high radiosensitivity of undifferentiated cells has been recognized since the early observations of Bergonié and Tribondeau (85) and, like the radiosensitivity of cancer cells, has been correlated with high nucleic acid content (86, 87).

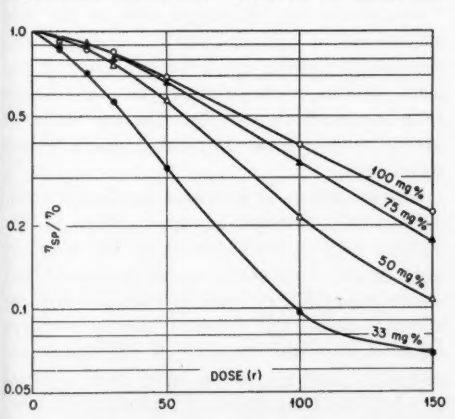

FIG. 5. Specific viscosity (Nsp/No) of x-irradiated rat thymus deoxynucleoprotein in 1.43 M NaCl (W. D. Fisher, unpublished data).

In view of the influence of oxygen tension, temperature and metabolic factors on the radiosensitivity of cells it is not surprising that the sensitivity of a tissue varies with its *vascularity* and *blood flow*. The importance of these factors in the radiocurability of cancer is apparent when it is recalled that tumor tissue is frequently poorly vascularized and hence to that extent relatively radioresistant (88). Other variables related to vascularity, such as water content, may also affect radiosensitivity (59, 71).

Influence of Radiation Factors. As mentioned earlier, chromosomal aberrations are rarely produced by a single photon because their production requires a relatively large number of ions or radicals acting simultaneously within a small volume. It follows, therefore, that it is not only the total dose of radiation absorbed (number of ions produced) but also the distribution of the dose in time (dose rate, or radiation intensity) and its distribution in the cell (ions per unit path of the radiation, or linear energy transfer) that determine the biological effects of the radiation. If a dose is administered in multiple exposures, depending on the dose per exposure and the interval between exposures, certain types of injury may be substantially repaired between treatments.

Accordingly, to minimize the injurious effects of irradiation on normal tissue (skin, bowel, hemopoietic organs), therapeutic radiation is usually administered in successive small doses, so as not to exceed the tolerance of the patient. Selection of optimal conditions for the treatment of each particular neoplasm (complicated by un-

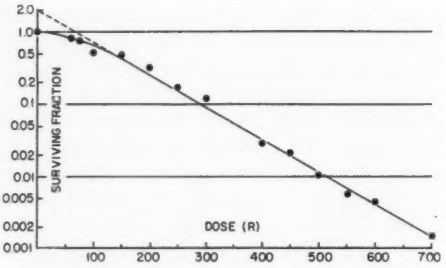

FIG. 6. Effects of x-rays on survival of reproductive ability in isolated HeLa cells (Puck and Marcus, ref. 40).

explained variations from patient to patient in the behavior of the same types of cells) requires more information about the influence of the various radiation factors than is now available.

As regards dose rate, there are still few quantitative data on the response of normal and neoplastic mammalian cells. A wide variety of experiments have been carried out with many kinds of biological materials and with certain human tissues, notably skin. The results of these studies, summarized by Paterson (59), indicate a complex interaction of the following variables: total dose, total duration of exposure, dose per fractional treatment, dose rate per treatment, interval between fractional treatments and rate of recovery from radiation injury inherent in the tissue irradiated. In no instance is the interaction of these factors adequately understood as yet; hence, more needs to be known about these variables for all types of neoplasms and for all types of normal cells. The complexity of the problem is illustrated by the observations that for certain responses, an enhanced effect of radiation is seen with fractionation at critical intervals (59, 89) and that the rate of recovery from radiation injury is influenced not only by the extent of the initial damage (90) but also by genetic factors (91).

The quality, or linear energy transfer (LET), of a given radiation also influences its relative biological effectiveness (RBE), presumably because it determines the distribution of ions or radicals formed within the cell. For the killing of most normal and malignant cells, RBE increases with LET, up to the LET level of fission neutrons (92, 93). In theory, therefore, to obtain the greatest lethality per unit dose of radiation, one should irradiate with heavy particles. The few attempts at radiotherapy with fast neutrons, however, have not been encouraging because of damage to normal tissue, particularly cumulative and delayed reactions (94). A means of localizing particulate radiation in tumors to avoid injuring normal tissue is being sought through neutron capture therapy, in which α-particle-emitting reactions are initiated by the capture of thermal neutrons in boron or lithium (95). This method is being explored in the treatment of inoperable human brain tumors by exposing the brain to thermal neutrons after boron compounds have been concentrated in the neoplasm (96). As yet, however, an adequately selective distribution of boron in the tumor cells has not been achieved, and the ultimate value of the method is uncertain. A perhaps more immediately promising approach is the use of high-energy proton and deuteron beams, which have the desirable properties of pencil-like focus, small entry dose, relatively little scatter, deep penetration and sharply localized absorption (fig. 9). Preliminary results with such beams have suggested their applicability to tumor therapy (97).

Efforts to localize radiation in cancer cells through the use of isotopes have not yielded dramatic results to date. I^{131}, however, is widely used in the treatment of certain types of thyroid malignancy, P^{32} in the management of polycythemia and some forms of leukemia and colloidal Au^{197} and $CrP^{32}O_4$ in the control of malignant serous effusions; in addition, other uses of isotopes are under investigation (97).

The growing use of supervoltage x-rays and gamma rays in radiotherapy despite their relatively low RBE, stems from their superiority over low-energy x-rays in penetrating power and scatter. With the former radiations a greater dose may be delivered to deep-seated tumors, relative to that absorbed in surrounding tissues and skin. Although this has diminished some of the side effects and symptomatology of therapy and increased the effective dose to cancer cells, it has made reaction of deep tissues a greater problem than heretofore. As yet, therefore, the extent of over-all improvement in results cannot be assessed (98).

Indirect Effects of Radiation on Cancer Cells. The action of radiation on cancer cells *in vivo*, in addition to its direct effects, is thought to result in large part from effects on the tumor bed and on the tumor-bearing host. The relation of these effects to one another, however, and their relative importance in the response of the tumor are uncertain. Indirect effects have been grouped into four main categories: *1*) leukocytic reaction, *2*) stromal reaction, *3*) vascular reaction and *4*) histolytic effects (46).

The *leukocytic infiltration* of irradiated tumors,

of doubtful specificity for irradiated cancer cells (99), may actually represent no more than a nonspecific inflammatory reaction to injured tissue. It has been postulated, however, that the prevalence of lymphocytes in the inflammatory infiltrate denotes an immunologic reaction, in part because of the association between immunity to grafted tumors and radiation-induced changes in local and circulating lymphocytes (100). Also attributed by some investigators to an 'immunizing' action of radiation are the observations that *1*) the growth of a transplanted tumor may be inhibited by localized irradiation of the recipient site prior to implantation (101, 102); *2*) irradiation of tumor cells *in vivo* may inhibit their growth on subsequent transplantation into a new host, the degree of inhibition varying with the interval between irradiation and transplantation (101); *3*) irradiation of the area surrounding a tumor, without exposure of the tumor itself, may cause regression of the neoplasm under certain conditions (103); and *4*) untreated metastases of transplanted tumors may regress after irradiation of the primary implant (104, 105). In commenting on some of these and related findings, Goldfeder (106) has emphasized that the so-called 'immunizing' action of radiation probably depends on the existence of some degree of histoincompatibility between tumor and recipient. Accordingly, the significance of these observations for the radiation response of primary neoplasms is uncertain, since the importance of immunogenetic factors in primary, as opposed to transplanted, cancer is not yet established (107). Furthermore, in many instances, other indirect effects may be involved in the 'immunizing' action of radiation.

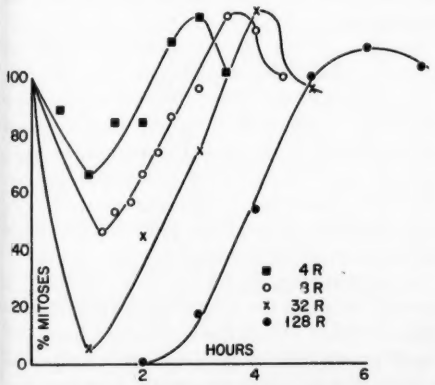

FIG. 7. X-ray-induced mitotic depression and 'overshooting' in cells of rat corneal epithelium (J. S. Friedenwald and S. Sigelman, *Exper. Cell Res.* 4: 1, 1953).

The potential influence of the connective tissue *stroma* of the tumor bed on the response of the tumor cells to irradiation has been mentioned repeatedly (52). In general, not only does the responsiveness of the tumor vary with the denseness of its stroma, but fibrosis of the stroma occurs in response to irradiation to a greater extent with radiosensitive than with radioresistant tumors (52, 105, 108). This stromal reaction, which is accompanied initially by inflammation, is believed to favor regression of the neoplasm, and since it is more pronounced in the zone adjacent to irradiated tissue than in the region directly exposed, irradiation through sieve-like filters has been used to promote its development (52). Although the mechanism of the reaction is unknown, the influence of genetic (109) and dietary (110) factors has been noted.

Because tumor cells are dependent on their blood supply for oxygen and other metabolites, *vascular* alterations caused by irradiation are not without effect. The relative importance of the vascular reaction, however, and its relation to the stromal changes have not been adequately assessed. A variety of effects of radiation on blood vessels have been described (111), from minor changes in permeability to swelling and necrosis of endothelial cells, with thrombosis. It has also been observed that irradiation inhibits the growth of capillary buds and thus interferes with the vascularization of transplanted tumors (112). The secondary, delayed degeneration of tumor cells irradiated *in vivo*, contrasted with recovery of cells simultaneously irradiated *in vitro*, has been ascribed to radiation-induced vascular insufficiency (54). Other experimental evidence (113), in addition to the relatively poor responsiveness of tumors in the presence of edema or inflammation of the tumor bed, points toward the importance of vascular factors.

The *histolytic effect* of irradiation consists of the breakdown of injured tissue, with release of substances ('nechrohormones') potentially toxic to surviving tumor cells. It is postulated that through this mechanism the original radiation damage may be secondarily amplified. Although hyperuricemia and signs of systemic intoxication may follow massive destruction of tissue by irradiation *in vivo*, the growth of transplanted tumors has not been found to be affected by high local concentrations of implanted dead tumor tissue (114). It has been noted, however, that the reaction of normal skin to irradiation is related to the size of the treatment field or volume of

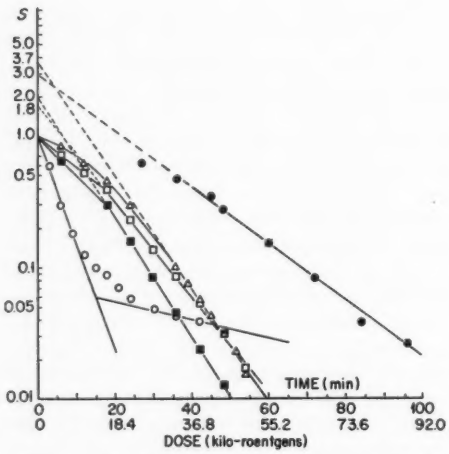

FIG. 8. Survival of x-irradiated yeast cells in relation to ploidy (Lucke and Sarachek, ref. 62). ○, Haploid (13,894), slope = 0.19; ■, diploid (11,296), slope = 0.11; □, diploid (11,294), slope = 0.086; ●, triploid (13,894 × 11,294), slope = 0.050; △, tetraploid (11,294 × 11,296), slope = 0.10.

tissue included in the beam; the larger the area exposed or the closer together two adjacent exposed areas, the greater the reaction per unit dose. This has led to the hypothesis that a toxic diffusible substance is released from the injured cells and that the surrounding normal tissue facilitates removal of this material and repair of the damage (115, 116). If such a diffusible substance does exist, its nature remains unknown; however, the possibility that it is histamine has been suggested (117). Another type of indirect effect, possibly related to the latter, is the observation that regression of a locally irradiated tumor may be enhanced by small amounts of radiation to the whole body, 50 r sufficing to elicit the maximal systemic response (118).

In any consideration of indirect action, it must not be forgotten, of course, that irradiation may influence the growth of tumor cells by effects on nutritional, endocrine, immunologic or physiologic status of the tumor-bearing host. The nature and magnitude of these effects will vary, in general, with the region of the body irradiated, the total volume of tissue exposed and the amount of radiation absorbed (119, 120).

Development of Radioresistance. It is a commonplace and clinically vexing property of tumors that their radiosensitivity diminishes progressively with repeated exposures to sublethal amounts of radiation. There has been much speculation about the mechanism of this phenomenon, which, in brief, may be ascribed to either a change in the inherent radiosensitivity of the tumor cells or alterations in the tumor bed or tumor-host relation.

It has been proposed that sublethal irradiation may increase the resistance of the tumor itself by killing all but the most radioresistant cells in an initially heterogeneous population. It has been suggested that through the same mechanism there may be selection of cells rendered resistant by radiation-induced mutations. This hypothesis, invoking a process analogous in some ways to that accounting for the emergence of drug-resistant strains of bacteria (121) and leukemic cells (122), has been tested experimentally under a variety of conditions. Resistance to radiation has been enhanced in this manner in bacteria (123) and apparently also in at least two transplanted mouse tumors (21; and W. St. Amand, 1958, personal communication). In a transplanted rat sarcoma, such resistance was observed after transplantation into new hosts to be associated with retarded growth and fibrosis of stroma (124). It is not clear whether in any of these experiments the acquired resistance was accompanied by chromosomal changes, such as polyploidy, or by metabolic alterations in the tumor cells. The possible relation between the acquired resistance of neoplasms and that of previously irradiated normal laryngeal (125) and intestinal (126) epithelium remains to be established.

In the majority of instances in which radioresistance was induced experimentally in a tumor by sublethal irradiation, it has not persisted after transplantation of the tumor into a new host; from which it has been concluded that the resistance did not reside in the tumor cells themselves but rather in the tumor bed (47, 127, 128). Similarly, in an experiment in which an ascites tumor was irradiated continuously throughout at least fifty cell generations under conditions designed to maximize the likelihood of selection of a radioresistant mutant, no such mutant was obtained (129). It would appear, therefore, that selection of resistant tumor cells, if and when it occurs, is probably not the major mechanism for development of radioresistance.

In addition to affecting the radiosensitivity of tumors, radiation has been observed to influence their virulence. Small doses of x-rays have rendered tumors able to grow in histoincompatible recipients (130), suggesting immunogenetic alteration or 'adaptation' of tumor cells of a type similar to that noted under other conditions (131, 132). Perhaps related to this phenomenon is the

observation that pulmonary metastasis of a tumor may be promoted if it is subjected to sublethal irradiation shortly after its implantation (133), although changes in the tumor bed cannot be overlooked as a mechanism of this effect.

In contrast to the reduced sensitivity usually caused by irradiation, a spontaneous mutation toward increased radiosensitivity has been reported in a C3H mouse mammary carcinoma, owing to increased antigenicity (134). This demonstrates the complex and variable nature of the influence of genetic factors on radiosensitivity.

Therapeutic Modification of the Radiation Response. To increase the effectiveness of radiation in the treatment of cancer, and hence to raise the cure rate, a number of measures have been used as adjuncts to conventional radiotherapy (135). These act, in general, by *1*) enhancing the radiosensitivity of tumor cells, *2*) increasing the amount of radiation tolerated by the host (through reducing the radiosensitivity of normal host tissues or promoting their recovery from radiation injury) or *3*) exerting a carcinostatic action on the tumor, which is additive or synergistic with that of the radiation itself.

Of the various *radiosensitizing* agents studied to date, oxygen has received the greatest attention; its role has already been mentioned. Evidence suggesting hypoxia of poorly vascularized tumor tissue (88) has prompted irradiation of cancer patients under increased oxygen tension and increased atmospheric pressure. It is postulated that these conditions do not significantly enhance the radiosensitivity of well-vascularized tissues, which are normally oxygenated to nearly optimal levels, but do heighten the radiosensitivity of poorly vascularized tumor tissue, thus increasing the effectiveness of the radiation. Results with a variety of experimental tumors and with selected human cancers verify this hypothesis (135). As yet, however, the method has not had adequate clinical trial to indicate its ultimate usefulness. Various other agents have also been reported to act as radiosensitizers, including synkavit, fluorescene, H_2O_2, inorganic salts, glucose and isulin. The effects of these agents are inconsistent, however, and require further evaluation (135).

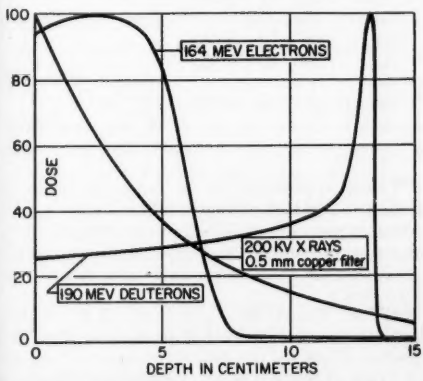

FIG. 9. Depth-dose distribution of 200 kv x-rays, 16.4 Mev electrons, and 190 Mev deuterons (Lawrence and Tobias, ref. 97).

Use of *radioprotective* and *recovery-promoting* agents to raise the radiation tolerance of the cancer-bearing host has been limited thus far, although a wide variety of substances have been used in palliation of radiation sickness. The development of potent radiation dose-reducing compounds, such as S,2-aminoethylisothiuronium·Br·HBr (AET)—which nearly doubles the $LD_{50}/30$ days of x-rays in mice (136), has prompted exploratory use of these agents in radiotherapy. Preliminary experiments with mice bearing disseminated transplanted leukemias and ascites tumors suggest that otherwise lethal doses of whole-body x-radiation administered after AET treatment induce better remissions than lower doses of radiation alone (A. D. Conger, E. E. Schwartz, R. Shapira, D. G. Doherty, 1958, unpublished data). Similar results have been obtained with the combined use of AET and nitrogen mustard (M. G. Kelly, R. W. O'Gara, D. P. Rall, C. G. Zubrod, 1958, unpublished data). These effects, which suggest that AET protects the host to a greater degree than the neoplasm, are logical in view of the higher concentration of AET in normal hemopoietic and intestinal tissues than in the neoplasms studied to date (D. G. Doherty, R. Shapira, A. D. Conger, E. E. Schwartz, 1958, unpublished data). Although preliminary results indicate that the relatively high toxicity of AET for man will interfere with use of this particular compound in clinical radiotherapy, other less-toxic radioprotective chemicals under investigation may prove to be clinically useful.

Because the radiosensitivity of the bone marrow limits the amount of radiation that can be tolerated when all or a major part of the body is exposed, it is highly significant that injury of hemopoietic tissue may be repaired by transplantation of a few nonirradiated, viable marrow cells (137). With the use of marrow transplantation, it is now possible to administer doses of total-body x-radiation large enough to afford

promise of curing generalized leukemia in laboratory animals (138–140). Since, however, the maximum tolerated dose of radiation is increased by a factor of only about 2.0 through the use of bone marrow, only relatively radiosensitive leukemias have thus far been cured by this attack (48; and E. E. Schwartz, C. C. Congdon, A. C. Upton, 1958, unpublished data). Furthermore, there is a relatively high mortality from delayed immune reactions in animals implanted with immunogenetically foreign marrow (141). Hence, this complication, if it occurs in human recipients and unless it can be controlled, will seriously limit the value of the procedure. At present, although marrow transplantation is being explored in carefully selected patients with leukemia (142), its evaluation must be postponed until more is known about the optimal doses of radiation and of marrow cells to be used in man and about the techniques of procurement and processing of human marrow. It is noteworthy that the effects of bone marrow are additive with those of AET, combined protection with both agents increasing by a factor of 2.5 to 3.0 the amount of whole-body radiation tolerated by mice (143), and that agents of these types also inhibit the delayed effects of irradiation, such as carcinogenesis and shortening of the life span (144).

A wide variety of *carcinostatic* agents have been administered with radiation in an effort to obtain additive or synergistic effects on neoplastic cells. These compounds include colchicine, antibiotics, arsenicals, urethane, purine analogues, alkylating agents and miscellaneous chemicals (135). The effects of these drugs have been variable; in some instances their use has enhanced the effectiveness of radiotherapy; in others little or no additional carcinostatic action has been detected. In many cases exploitation of combined therapy has been hampered by combined toxicity. Although few combinations have been thoroughly evaluated, some appear clinically promising (135). On theoretical grounds, the value of combined treatment is suggested by *a*) the importance of nutritional factors in the recovery of bacterial cells from radiation injury (145), *b*) the manifest advantages of combinations of chemotherapeutic agents in the treatment of leukemia (146), *c*) the ability of combined agents to attack cells in differing stages of division and through diverse mechanisms (70) and *d*) the known synergism between radiation and radiomimetic chemicals in the production of chromosomal aberrations and related genetic damage (147).

CARCINOGENIC EFFECTS OF RADIATION

Historical Observations. It is now established that neoplasms of virtually all types may be induced by radiation and there are no significant qualitative differences in the carcinogenic effects of the various kinds of ionizing radiations (148). Although the most extensive and most quantitative data on radiation carcinogenesis have been obtained from systematic experimentation with laboratory animals, the carcinogenic effects of radiation have been conclusively demonstrated in man. The following examples are of historical interest: *a*) *Cancer of the skin:* before it was realized that cumulative exposure of the skin would lead eventually to an irreversible type of injury known as radiation dermatitis, many of the early radiation workers inadvertently overexposed their hands through prolonged manipulation of radiation equipment. The development of squamous cell carcinoma as a complication of radiation dermatitis cost the lives of scores of these pioneers (149). *b*) *Leukemia:* this disease, recognized early in this century as a potential hazard of irradiation (4), is far more prevalent in the heavily irradiated Japanese atomic bomb survivors and in patients treated by radiotherapy

TABLE 1. INCIDENCE OF LEUKEMIA IN PATIENTS TREATED WITH X-RAYS FOR ANKYLOSING SPONDYLITIS AND IN JAPANESE ATOMIC BOMB SURVIVORS IN HIROSHIMA

Av. Max. Dose of Radiation, r*	Spondylitis Patients†			Hiroshima Survivors‡		
	No. of men exposed	Men with leukemia		No. of survivors	Survivors with leukemia	
		No.	%		No.	%
2250	290	6	2.068			
1750	805	4	0.497			
1300				1,200	16	1.33
1250	3062	11	0.359			
750	4180	10	0.239			
500				10,500	28	0.266
250	2861	4	0.139			
50				18,700	6	0.032
5				67,700	10	0.015

* Crude approximation of radiation dose, according to method of Lewis (157). Because these estimates are subject to large error, they are considered to provide at best only a semiquantitative correlation between leukemia incidence and radiation dose.

† W. M. Court Brown and R. Doll, *Medical Research Council Special Report Series* No. 295. London: H. M. S. O., 1957.

‡ From: Committee on Pathologic Effects of Atomic Radiation. *Pathologic Effects of Atomic Radiation*, Nat. Acad. Sc.–Natl. Research Council, Publ. No. 452, 1956.

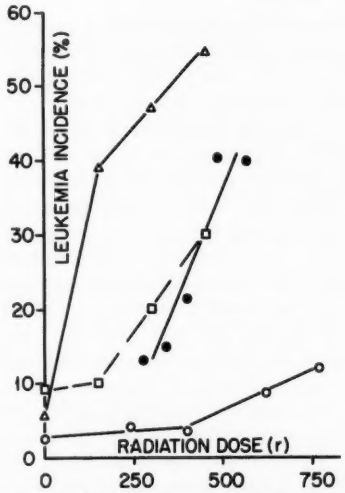

FIG. 10. Relation between leukemia incidence and radiation dose in mice of several strains. △, Myeloid leukemia in RF mice (A. C. Upton, F. F. Wolff, J. Furth and A. W. Kimball, *Cancer Res.* In press). □, Lymphomatosis (thymic) in RF mice (*ibid.*). ○, Lymphomatosis (thymic) in LAF_1 mice (J. Furth, A. C. Upton, K. W. Christenberry, W. H. Benedict and J. Moshman, *Radiology* 63: 562, 1954). ●, Lymphomatosis (thymic) in C57BL mice (Kaplan and Brown, ref. 89).

for spondylitis than in the population at large (table 1); its incidence is also elevated in radiologists (150), in those irradiated for thymic enlargement in infancy (151) and perhaps even in those exposed to diagnostic radiography *in utero* (152). *c*) *Osteosarcoma:* the induction of bone tumors, first noted among watch dial painters, was seen to occur in areas of skeletal damage caused by locally deposited radium (153). The frequent occurrence of this complication after ingestion of radium and its daughter elements has since been well documented in many additional victims (154).

Tumor Incidence Versus Dose. The relation between tumor yield and radiation dose varies with the kinds of tumors induced, with genetic differences in susceptibility (species, strain), with physiological variables (age, sex, hormonal activity), and with radiation factors (region of the body irradiated, dose rate, dose fractionation, linear energy transfer). Furthermore, susceptibility to the carcinogenic action of radiation is not necessarily correlated with susceptibility to the spontaneous development of cancer or to the carcinogenic action of other agents (155). The combined tumor-inducing effects of radiation and chemical carcinogens are often additive, but in some instances the reverse has been noted (156). In general, although the incidence of neoplasms varies with the amount of radiation absorbed, it is not known whether there is a threshold dose for carcinogenesis. Evidence suggesting the absence of a significant threshold has been presented for leukemia induction in man (157); however, it is apparent that the dose-response curve is not linear for leukemia induction in mice (fig. 10), and the incidence of some types of the disease in man is not greatly affected by radiation (E. E. Schwartz and A. C. Upton, 1958, unpublished data).

Mechanisms of Carcinogenesis. Despite extensive investigation of radiation-induced neoplasia in a variety of species, the mechanism of tumor formation remains unknown. Also largely unknown are the events preceding the appearance of malignant growth, although the period intervening between irradiation and the earliest detectable evidence of cancer is characteristically long in relation to the life span (3–30 months in mice, 3–30 years in man). To account for this delay, which varies inversely with dose, a multistage process has been postulated by some investigators similar to that proposed by others to explain the chemical induction (158) and spontaneous development (159) of neoplasia. According to this theory, irradiation initiates the cancer change by irreversibly altering a cell in a way that predisposes it to further alteration by growth-promoting forces in its environment (160). The acquisition of malignant properties by such an altered cell occurs gradually, therefore, and is potentiated by growth-stimulating factors that may be present naturally in the host. For example, in the induction of ovarian tumors by irradiation, the importance of gonadotrophic stimulation is inferred from the fact that tumor formation is inhibited if one ovary is left intact or if a normal ovary is implanted or estrogen administered after irradiation (161, 162). Furthermore, Kaplan *et al.* (163) and Law and Potter (164) demonstrated that neoplasia may develop in a nonirradiated thymus if it is implanted in an irradiated recipient, indirect mechanisms being of tantamount importance in this situation since the cancer-forming cells themselves are not irradiated. Similarly, in the pathogenesis of certain radiation-induced endocrine tumors, indirect mechanisms involving effects on the host appear to be more important than direct effects of radiation on the cancer-forming cell (165). In radiation-induced endocrine tumors (165) and lymphomas (166) the evolution of malignancy

has actually been observed to occur in stepwise fashion, verifying that the cancer change is a multistage process in these instances. In the induction of other types of neoplasms, the action of promoting factors and the existence of separate stages in the development of malignancy have not been recognized, but whether this implies a different mechanism of radiocarcinogenesis cannot be decided without further evidence.

Whatever role disturbances of growth-regulating mechanisms in the host play in the neoplastic transformation of the cancer cell, it is clear that the final acquisition of malignant properties entails a permanent change in the cell itself, since the cancer cell grows autonomously on transplantation into a normal host. The nature of this cellular change is unknown, but its persistence through successive cell generations indicates a self-perpetuating abnormality. This suggests that the change may either reside in the genome of the cell as a somatic mutation or may denote the action of a transforming principle or virus.

The somatic mutation theory is an attractive mechanism to account for radiocarcinogenesis because of the known mutagenicity of ionizing radiation. As mentioned earlier, however, there are instances in which radiation-induced neoplasia may occur exclusively through indirect effects of radiation on the host and not through the mutagenic action of radiation on the cancer-forming cell itself. Although these instances do not exclude the possibility that carcinogenic mutation occurs through indirect effects or that under other conditions the carcinogenic effect of radiation may depend on its mutagenic properties *per se*, they do indicate that the latter is not necessarily the mechanism of radiation carcinogenesis. The association between mutagenicity and carcinogenicity in various chemicals has also been thought to favor the somatic mutation theory; however, this correlation is not without exceptions, and in no instance has the association between mutagenicity and carcinogenicity been demonstrated to be one of cause and effect (167). The implications of these and other similarities between radiation and chemical carcinogens have been reviewed by Haddow (168, 169).

The possibility that radiation may exert its carcinogenic action through a virus or transforming principle has received support from the discovery that filterable agents may cause leukemia and other neoplasms in mice (170–175). According to this theory, radiation may conceivably act through one of three mechanisms: *a*) it may convert a benign preexisting provirus to a carcinogenic provirus or virus; *b*) it may cause infection by an extraneous carcinogenic virus through depression of host immunity; *c*) it may lead to synthesis of a carcinogenic nucleic acid (transforming principle or virus) by disturbing normal nucleoprotein and chromosomal metabolism. Since the second mechanism would presumably require absorption of a relatively large amount of whole-body radiation within a short period of time, it cannot explain the carcinogenicity of small doses of radiation or chronic low-level irradiation. The first possibility, however, in view of the linear relation between radiation dose and lysogenicity in bacteria (28), can account theoretically for the carcinogenic effects of even the smallest doses, as can the third possibility. Furthermore, the virus theory is compatible, in general, with the effects of genetic, hormonal and age factors on susceptibility to radiocarcinogenesis (176) and with the virus-activating potency of carcinogenic agents (177). Although as yet largely speculative, the theory is amenable to experimental study and is currently under active investigation.

CONCLUSION

Through study of the effects of ionizing radiation, fundamental information has been gained about the biology of normal and neoplastic cells and about the process of neoplasia. A variety of disturbances have been observed in irradiated cells, including alterations in metabolism, growth and differentiation, but existing evidence suggests that the most significant primary action of radiation is on the genetic apparatus of the cell. That radiation-induced genetic effects may initiate tumor formation is highly conceivable; however, some other mechanism seems to be involved in certain instances of radiation carcinogenesis. Whatever the mechanism, the development of malignancy appears to be a complex, multistage process.

The material basis for the large variation in radiosensitivity that exists among cells of different types is still poorly understood; however, with increasing knowledge of the mode of action of radiation and of the factors influencing the radiosensitivity of the cell, ways are being found to increase, decrease and repair radiation injury. These advances offer promise of providing means of enhancing the effectiveness of radiotherapy in the treatment of cancer and of reducing the hazard of radiation as a carcinogenic agent.

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VIRUSES, GENES, AND CANCER[1]

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A MAJOR POINT AT ISSUE in the cancer field today (1, 2), as in the past, is whether the generality of cancers is caused by an intrinsic cellular change—a somatic mutation or alteration in the genes, in the nucleolus, or in the cytoplasmic particulates of somatic cells—or whether the generality of cancers is caused by the action on cells of an extrinsic factor—such as a virus. It is with this perspective in mind that I have chosen to speak about viruses, genes, and cancer. While my discussion will concern principally the viruses, my intention is not so much to favor one concept of cancer causation over the other but rather to examine some of the evidence for both. As you will see, these conflicting views of cancer causation appear to converge and to become essentially inseparable, at least in one neoplastic system thus far studied.

This year marks the fiftieth anniversary of the discovery by Ellerman and Bang (3) that leukemia of fowl could be transmitted from one chicken to another by the injection of cell-free filtrates of blood. Rous (4) in 1910 proved that a malignant solid tumor, a sarcoma of the common fowl, could be transmitted by a filterable agent, separable from the tumor cells and thenceforth called a 'tumor agent.' Among some forty spontaneous tumors of fowl studied by Rous and his associates during this early period, five types of mesenchymal cancers were found to be transmissible by cell-free filtrates. In the following years additional kinds of virus-induced tumors of the chicken were discovered, among them a broad category which is designated avian leukosis complex. The frequency of this disease is shown by the financial loss born by the poultry industry in the United States and attributed to it, in 1951 estimated to be approximately $75,000,000.

The concept of the virus etiology of neoplasms was extended to the mammalian kingdom by the studies of Shope (5), reported in 1933. He showed that cutaneous epithelial papillomas were transmissible to both wild and domestic rabbits by cell-free filtrates prepared from naturally occurring papillomas of wild rabbits. Within the next two years, Rous and Beard (6) reported that in many instances the virus-induced rabbit papillomas progressed to epithelial cancers.

The role of a filterable agent in the etiology of mammary carcinoma in certain strains of mice was demonstrated by Bittner (7) and his associates in work carried out on the milk agent or the milk factor since 1936. There are a few additional reports of virus-induced neoplasms in mammals, of which the latest is the transmissible leukemia of mice described by Charlotte Friend (8) in 1956. Among the amphibia, the renal carcinoma of the leopard frog, first studied by Lucké (9), is probably caused by a virus.

Depending upon the point of emphasis, the position might be taken that there has been remarkable little success, considering the numerous attempts that must have been made during the last half-century, in recovering viruses from the generality of cancers of experimental animals and man; or the obverse position might be taken, that the successes are more relevant to the overall problem of cancer etiology than are the failures and that the established fact of virus etiology of a few cancers should command more attention than does pure speculation regarding the etiology of most of all the other cancers. The viruses are the principal biological agents in cancer causation in lower animals; and in fact the most common cancers of fowl and possibly also of mice are caused by viruses. There are also some cancers in man in which, considering certain clinical and pathological findings, the possibility of virus causation is a recurrent topic of discussion. I refer, e.g., to acute leukemias and Hodgkin's disease.

Much of general and special interest in biology, pathology, immunology and biochemistry has been learned by the study of viral oncogenesis. Foremost perhaps is the fact, ascertained from the study of the Rous sarcoma and certain leukemias of fowl, that some viruses can induce the transformation to cancer within less than one

[1] This work was supported by grants from the National Cancer Institute, Public Health Service, and the Damon Runyon Memorial Fund.

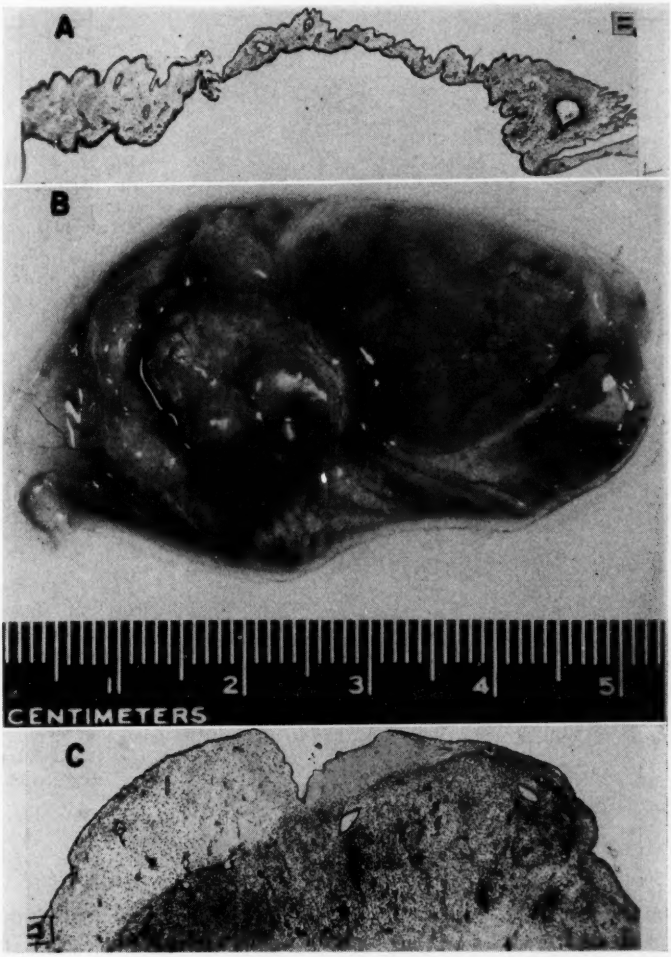

FIG. 1. *A*. Normal chorioallantoic membrane of chick embryo. Hematoxylin-eosin section. 22×
B. Rous sarcoma in chorioallantoic membrane. *C*. Rous sarcoma in chorioallantoic membrane. Hematoxylin-eosin section. 22×. (Material courtesy of Dr. Spencer Munroe.)

week's time, a rapidity of action that is unequalled by any other carcinogenic agent.

The specificity of action of oncogenic viruses is also a characteristic attribute. Each filterable agent gives rise for the most part only to neoplasms of the same kind as that from which it was derived and thus displays very narrow cytotropism. The Rous virus infects mesenchymal cells of the fowl, the Shope papilloma virus infects squamous cells of the rabbit epidermis but not those of mucous membranes (10), and so on. A corollary of narrow cytotropism is that a multiplicity of cancer types, as in man, where cancers arise from practically every type of cell in the body, would apparently require also an equal number of cancer viruses. Variation, however, is a property of the generality of viruses and is found also in the oncogenic viruses. For example, Duran-Reynals (11) has shown that the inoculation of Rous virus into ducks results in the production of neoplasms with new characters; or again it has been shown that a spectrum of changes—hemorrhagic, necrotizing, inflammatory, proliferative, and truly neoplastic—may be produced by certain of the oncogenic viruses, depending principally upon such host factors as species and age.

Immunity to oncogenic viruses may be natural or acquired. The milk agent of mouse mammary carcinoma is anomalous in that it has little or no

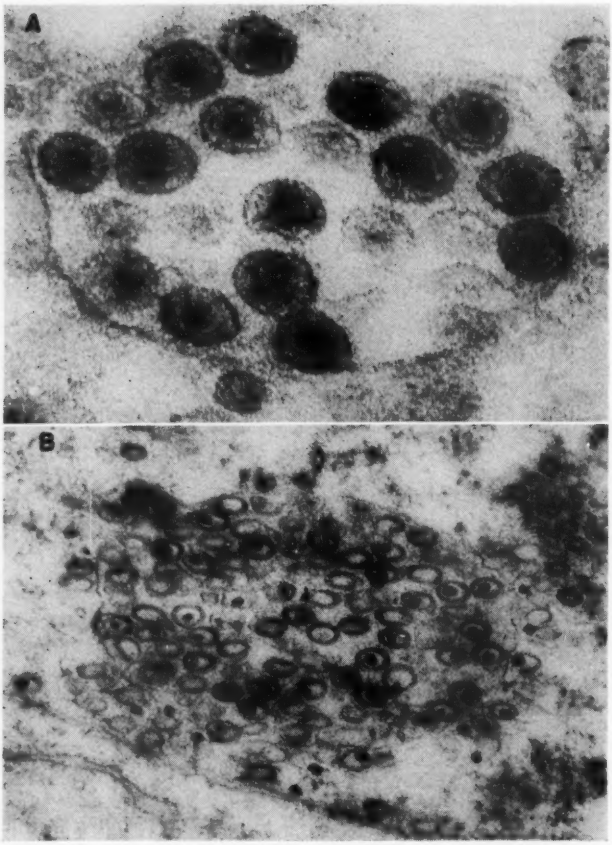

FIG. 2. *A*. Rous sarcoma virus particles in cytoplasmic vacuole. Ultrathin section. Electron micrograph, 146,500×. (Courtesy of Dr. Charles Oberling, ref. 21.)

FIG. 2. *B*. Virus-like particles in Lucké adenocarcinoma. Ultrathin section. Electron micrograph, 48,400×. (Courtesy of Dr. Don Fawcett, ref. 24.)

antigenic activity in mice. A high titer of antiviral antibody is present in the serum of a fowl bearing a regressing Rous sarcoma, or after such a sarcoma has disappeared. A rabbit bearing a Shope papilloma develops antibodies which will neutralize Shope virus *in vitro* or fix complement in mixture with it. As noted previously, some of the Shope papillomas progress to epithelial cancers. Kidd and Rous (12) have serially transplanted some of these papilloma-derived carcinomas in domestic rabbits and observed that the cancer grafts also immunize the host against Shope virus. The Vx2 and the Vx7 carcinomas were notable in that a graft of the former had lost the power to immunize against Shope virus by the 46th generation of transplantation (13), whereas a graft of the Vx7, as we have recently ascertained, continued to immunize against Shope virus at the 48th generation. The relevant question is raised as to how virus is propagated in cells in the presence of a high titer of circulating antibodies. The explanation, for which evidence has been presented by Rous, is that the tumor cell is really the host of the tumor virus, safeguarding it against inactivation by antibodies and providing it by cellular division with an endless succession of new hosts.

Another question, one of far-reaching significance, raised by the study of the oncogenic viruses but not unique for them is the loss of filterability or recoverability of virus under certain circumstances. Shope, in his original study of infectious papillomatosis of rabbits (5), showed that virus was regularly recovered in cell-free filtrates prepared from papillomas of wild rabbits but not from virus-induced papillomas of domestic rabbits. Yet the presence of virus, or of immunizing antigen, in domestic rabbits bearing Shope papillomas was shown by the partial or complete immunity of the domestic rabbit to

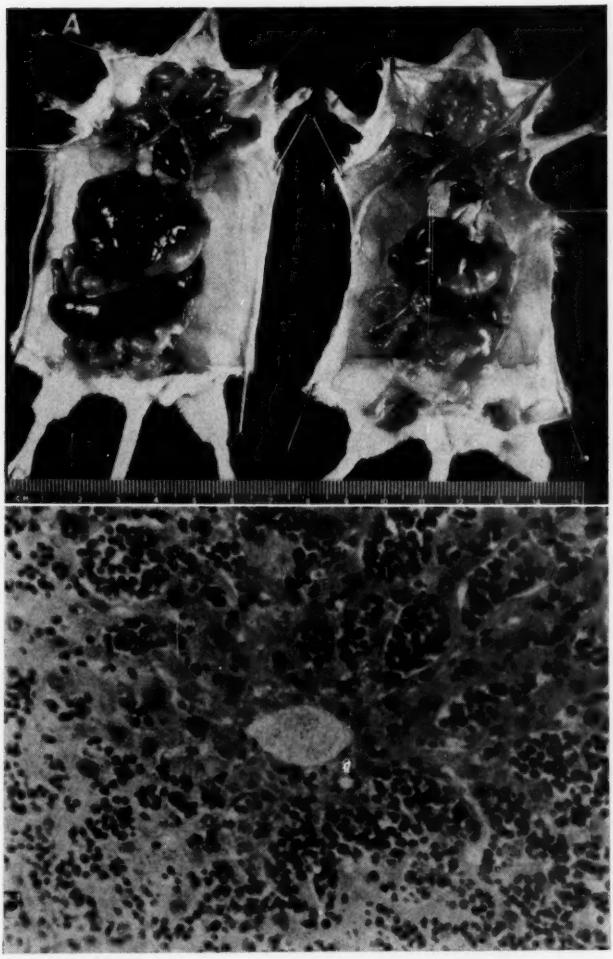

FIG. 3. *A*. Friend (virus) leukemia of mouse (*left*); and normal mouse for comparison (*right*). (Courtesy of Dr. Charlotte Friend, ref. 8.)

FIG. 3. *B*. Mouse liver infiltrated by Friend leukemia cells (dark-stained in the illustration). Hematoxylin-eosin section. 240×.

reinfection with Shope virus and by the presence of virus-neutralizing and complement-fixing (14) antibodies in their sera. Virus existing thus in a state not demonstrable by conventional methods of study was called masked virus by Shope (15). It is conceivable that virus could become masked or occult by combination with neutralizing antibodies; or by firm, undissociable union with cellular constituents; or by some other qualitative alteration. It is possible also, as Beard (16) maintains, that the explanation is principally quantitative. He has shown that papillomas of the domestic rabbit consistently contain much less virus than do papillomas of the wild rabbit and accordingly provide less favorable starting material for the recovery of virus. Newer methods are now available for the study of viruses in tissue sections, and these may eventually afford a better understanding of such host-virus relationships.

I would like now to comment briefly about the nature of intrinsic cellular changes in carcinogenesis. The essence of a cancer is the continued replication of the cells which compose it. This leads one to ask, what provides the driving force for perpetuating cell division through successive generations of cancer cells; or to ask the obverse, what restraining force for controlling cell division is lacking in the cancer process. One of the most important concepts in contemporary biological research may eventually contribute to the answer. This is the recognition that nucleic acids and proteins, mutually interdependent and sometimes bearing complementary structural configu-

rations, are intimately concerned in the fabrication of replicating structures such as genes and viruses (17). Accordingly, macromolecular complexes of nucleic acids and proteins, whether of viral or intrinsic origin, are thought to play a role, possibly a crucial one, in the genesis of cancer.

In the somatic mutation theory of carcinogenesis, changes are postulated to occur in the structure and the biological activity of chromosomes, or their submicroscopic constituents, the genes. The concept has been broadened in recent years to implicate cytoplasmic particulates and the nucleolus of the cell as well. The somatic mutation theory is considered by its proponents to receive support from the fact that during the course of repeated transfers, transplantable tumors may undergo abrupt changes, leading to more aggressive biological behavior in the strain of origin, to a greater range of transplantability in other strains, and to the acquisition of different (generally less differentiated) morphological features. These events simulate those expected from a mutation, which in the definition of a geneticist (18) is an hereditary change based upon sudden, and largely irreversible, changes in a chromosome set, an individual chromosome, a section of a chromosome, or a submicroscopic part of the chromosome, the gene.

There is another theory of cancer causation which may be called the immunological concept (19). Like the somatic mutation theory, it needs to muster scientific credentials. By postulating that the cells gain autonomy by the loss of surface antigens or 'identity' proteins, the immunological concept explains, quite as satisfactorily as does somatic mutation, the acquisition by tumors of more aggressive biological behavior, greater range of transplantability and so on. One of the commendable aspects of this theory is that it is,

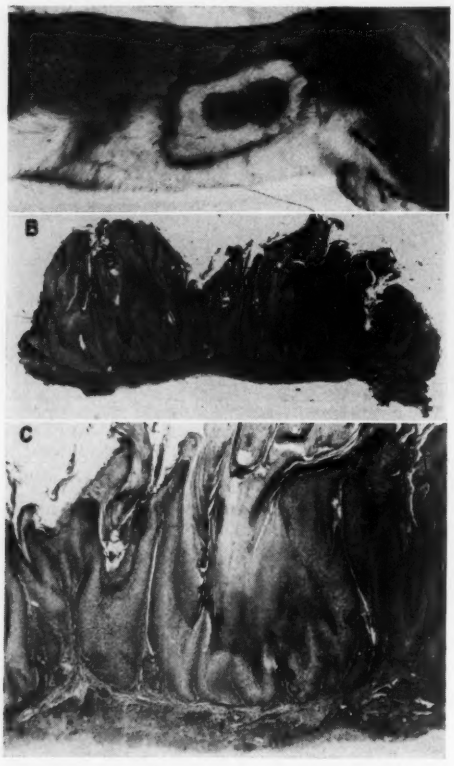

FIG. 4. *A*. Shope papilloma of domestic rabbit. *B*. Shope papilloma of cottontail rabbit. Hematoxylin-eosin. 6.1×. *C*. Shope papilloma of cottontail rabbit. Hematoxylin-eosin. 16×.

FIG. 5. *A*. Rabbit with skin squares showing effects of Shope papilloma virus and neutralizing antisera in mixture with it. (Courtesy of Dr. Peyton Rous, ref. 25.) *B*. Rabbit with tiny papilloma attesting to partial immunity to Shope papilloma virus conveyed by a graft of Vx7 carcinoma (in thigh muscle, not shown). Compare with fig. 4*A*, in which an identical inoculum of virus was used.

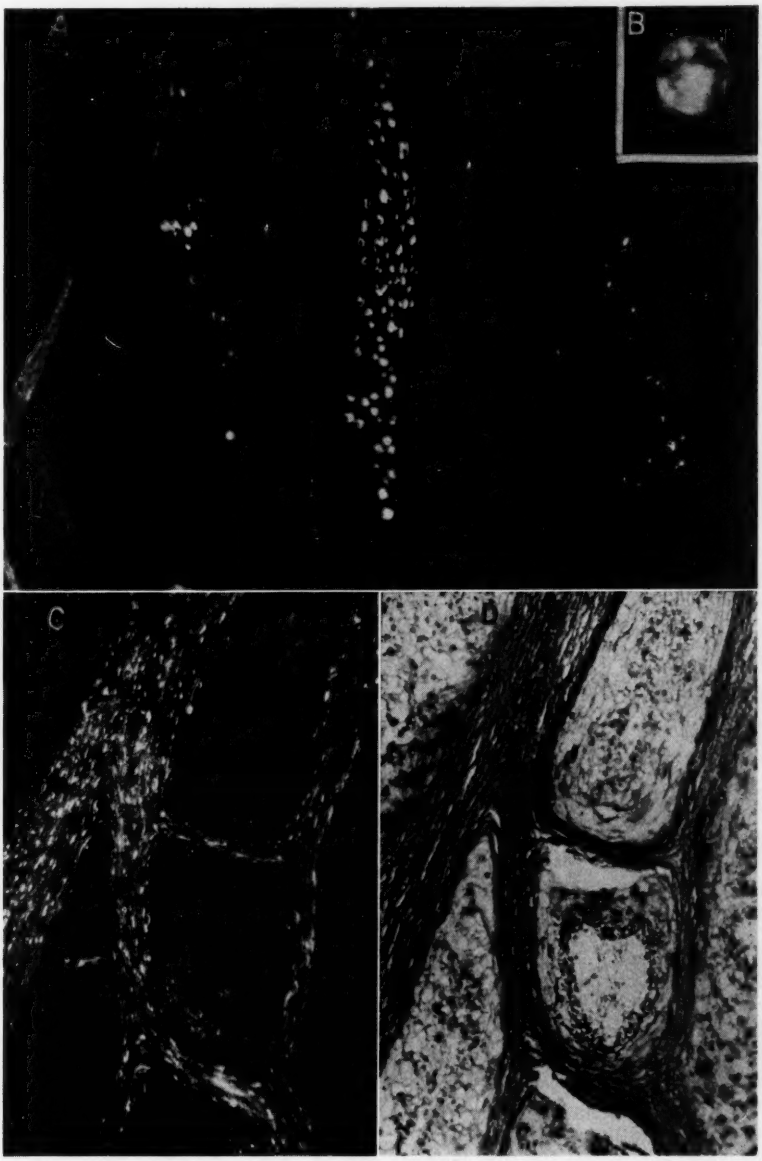

FIG. 6. *A*. Shope papilloma of cottontail rabbit stained with fluorescent antibody for Shope viral antigens. Frozen section. Fluorescence photomicrograph. 122×. *B*. Similar to *A*. 575 ×. *C*. Similar to *A*, but tangential section. 75×. *D*. Same section and field as *C*, after counterstaining with hematoxylin and eosin.

at least in part, capable of critical evaluation with immunological techniques. For example, by utilizing the Ouchterlony procedure for precipitin reactions in gel, Korngold (20) is able to contrast and compare soluble antigens of cancer cells, in respect to number and identity, with those of homologous normal cells.

The illustrations which now follow were selected to show some of the well-known biological attributes of virus-induced neoplasms in birds

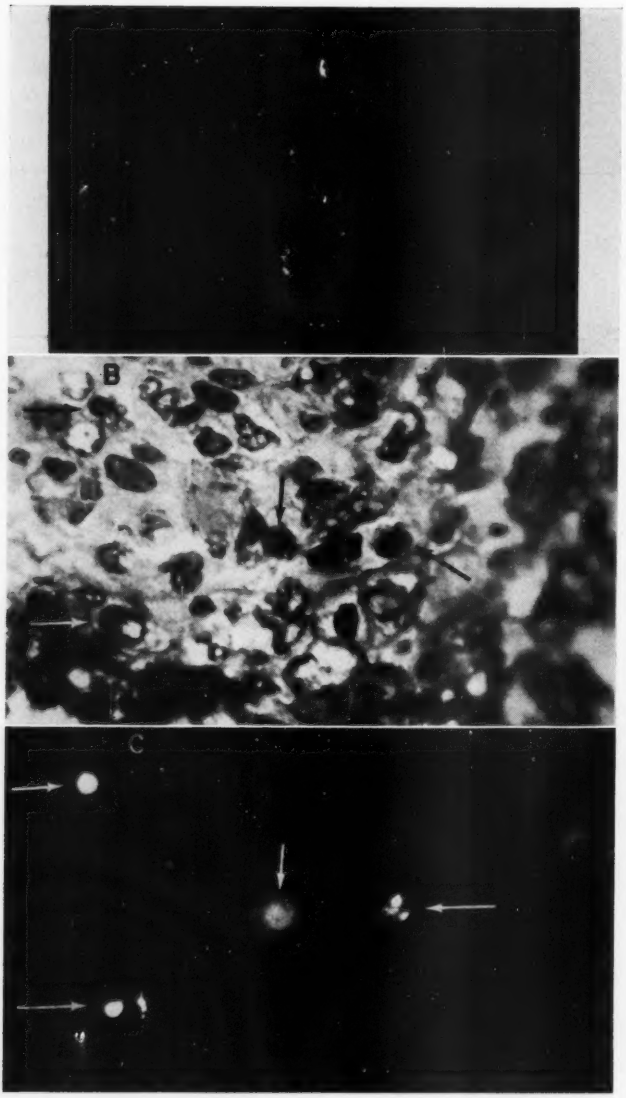

FIG. 7 *A*. Shope papilloma of domestic rabbit stained with fluorescent antibody for Shope viral antigens. Antigen (white area) present in nucleus of one cell and in trace amounts in another located in V-shaped keratinized area at surface. Frozen section. Fluorescence photomicrograph. 125×.

FIG. 7. *B* and *C*. *C*, V×7 carcinoma in domestic rabbit stained with fluorescent antibody for Shope viral antigens, and *B* same section and field as *C* after counterstaining with hematoxylin and eosin. Viral antigen (white areas) present in nuclei (or portions of nuclei) of only 4 carcinoma cells, the remaining cancer cells not containing detectable amounts. Frozen section. Fluorescence photomicrograph (*C*). 500×.

and rabbits and to illustrate applications of two modern analytical procedures (electron microscopy and fluorescent antibody) for the study of tumor viruses.

The rapidity of action of some of the oncogenic viruses has already been mentioned and is illustrated in figure 1. Figure 1*A* is a hematoxylin-eosin section of normal chorioallantoic membrane of the chick embryo, photographed at low magnification. One sees primitive mesenchyme lying between epithelialized surfaces. Figure 1*C* is a chorioallantoic membrane infiltrated and expanded by a cellular neoplasm. This is Rous sarcoma which had arisen and grown to macroscopic size, as in figure 1*B*, within 7 days after Dr. Spencer Munroe had inoculated the membrane with Rous sarcoma virus.

As you know, new chapters in the morphology of cells and viruses are being written with the aid of the electron microscope and ultrathin sections. Figure 2*A* which is an electron micrograph of a cytoplasmic vacuole in a Rous sarcoma cell has been kindly provided by Drs. Bernhard, Oberling and Vigier (21). At a magnification of 200,000×,

the Rous virus particles in the vacuole are seen to have internal structure consisting of a dense central body which in turn is surrounded by one or more dense limiting membranes. A similar ultrastructure has been found in the other types of avian oncogenic viruses thus far studied (22).

Structural variations in oncogenic viruses have been identified in electron micrographs of Shope fibroma (23) and Lucké adenocarcinoma (24). In the latter, mature virus particles are each composed of a dense central body enclosed by a dense double membrane; while central bodies without dense limiting membranes and vesicular membranes without inner bodies also exist (fig. 2*B*).

Figure 3*A* (left) is a gross illustration, kindly provided by Dr. Charlotte Friend, of a mouse with leukemia induced by Friend virus (8). Note the enlargement of liver and spleen of the leukemic mouse in comparison with the normal mouse (right). These and other organs, as well as the bone marrow, are infiltrated with leukemia cells (fig. 3*B*).

Figure 4*A* is the gross appearance of Shope papilloma in the domestic rabbit at one month after inoculation of the scarified skin with Shope papilloma virus. Two papillomas, formed by the coalescence of many smaller ones, have arisen in the skin and have hard, jagged and pigmented surfaces. As shown in a hematoxylin-eosin section at lower (fig. 4*B*) and higher (fig. 4*C*) magnifications, the Shope papillomas arise in the epidermis and are composed of three strata of epithelial cells which may be designated in respect to location as deep, intermediate and superficial, or in respect to cellular morphology as proliferating, keratohyaline and keratinized layers. The epithelial cells in the deeper layers increase in number by mitotic division and thus contribute to the growth of the papilloma. The cells of the intermediate and superficial layers cease to divide, form keratin and eventually die. A large part of the papilloma is thus composed of nonviable keratinized cells.

	Complete virus	Incomplete virus
Structure	◉	•
Composition		
Nucleic acid •	+	+
Protein ○	+	−
Biological		
Infectivity (cell to cell)	+	+
Transmissibility (host to host)	+	−
Proliferating cells	−	+
Keratohyaline cells	+	−
Keratinized cells	+	−

FIG. 8. Possible stages in the development of the Shope papilloma virus. Explanation in text.

The effectiveness of antisera obtained from rabbits bearing Shope papillomas in neutralizing the Shope papilloma virus is shown in figure 5*A*, kindly provided by Dr. Rous (25). Scarified skin squares of the rabbit were inoculated with papilloma virus, which by itself produced the largest mass of confluent papillomas but which in mixture with antiserum produced no papillomas in some instances, attesting to complete neutralization of the virus, while in others there were discrete papillomas in larger or smaller number. Rabbits bearing grafts of the papilloma-derived Vx7 carcinoma also have immunity to the Shope papilloma virus, and their sera contain virus-neutralizing and complement-fixing antibodies, as shown by the work of Rous and his associates (26). The domestic rabbit in figure 5*B* had received a 48th generation transplant of Vx7 carcinoma (in a thigh muscle, not illustrated) and 10 weeks later was challenged with Shope papilloma virus. As shown in the photograph, taken at one month after virus inoculation, one small papilloma had appeared after a prolonged latent period; whereas a nonimmune rabbit inoculated with the identical preparation and amount of virus had developed large papillomas by this time (fig. 4*A*) and these had appeared much earlier.

We have utilized immune sera of high titer obtained from papilloma-bearing (27) and Vx7 carcinoma-bearing (26) rabbits to prepare, following the method of Coons (28), fluorescent antibody stains for Shope viral antigens in papillomas of the cottontail (fig. 6) and the domestic rabbit (fig. 7*A*) and in the Vx7 carcinoma (fig. 7*C*) as well. In the fluorescent antibody procedure, sites of viral antigens are seen in characteristic apple-green color (white in the illustration) produced by the immunospecific deposition of fluorescein-labeled antibody. The cellular localization of Shope viral antigens, as demonstrated in the cottontail papilloma (fig. 6) with fluorescent antibody, was notable in these respects: viral antigen was present only in the nucleus of papilloma cells (fig. 6*B*); and viral antigen was localized almost exclusively in papilloma cells of the keratohyaline and keratinized layers (fig. 6*A*) and was essentially undetectable in cells of the

proliferating layer. The latter relation is shown to advantage by comparing a microscopic field of a tangential (horizontal) section of a cottontail papilloma after staining with fluorescent antibody for Shope viral antigen (fig. 6*C*) and after staining with hematoxylin and eosin (fig. 6*D*). The bright white areas in figure 6*C* indicate the distribution of Shope viral antigen; and the antigen localization corresponds to some of the nuclei of keratinized cells, cells whose cytoplasm stains pink with eosin and appears gray in figure 6*D*. The nuclei of some of the keratohyaline (or granular) cells (not shown in fig. 6*D*) also contain viral antigen. In cells of the proliferating layer viral antigen is rarely, if ever, detectable and exists at most in trace amounts.

Aside from this study, there has been no previous demonstration of the precise cellular localization of the Shope papilloma virus. Were it asked where one would expect to detect the virus, the answer would most likely be "In the proliferating cells of the papilloma if the virus has anything to do with the growth of the papilloma, and this appears undeniable." As you have seen, however, the proliferating cells do not contain detectable amounts of virus. Perhaps the multiplication of virus in these cells just keeps pace with the multiplication of the cells, so that detectable amounts of virus do not accumulate. When mitotic activity in the proliferating cells was decreased or arrested by treatment of the papilloma-bearing rabbit with colchicine or with x-rays, there was no demonstrable difference in the localization of virus. Perhaps antibodies enter the proliferating cells and coat the virus, thus interfering with the fluorescent antibody stain. That this appears not to be the case was shown by the failure to detect localized rabbit γ-globulin in these cells, using the appropriate fluorescent antibody stain. Perhaps the virus is present in the proliferating cells in a form not demonstrable with fluorescent antibody, existing in an incomplete or early stage of development and composed of deoxyribonucleic acid but deficient, or possibly totally lacking, in protein. In this view, the nucleic acid moiety of the virus may be the infective component, passing from cell to cell in the same host and stimulating mitosis; whereas, the protein moiety of the virus may, as a surface coating, for example, provide immunologic and cellular specificity and serve to preserve transmissibility of the virus to a new host.

This speculative concept of possible stages in the development of the Shope papilloma virus is summarized in figure 8. The structure of the complete virus or, more properly, of its surface molecules is symbolized by a dot, representing a nucleic acid core, and a circle, representing a protein shell. The protein shell is the serologically active component of the virus and is a determinant by surface interaction of the specific cellular affinities of the virus. The protein shell protects the infective nucleic acid core and serves to preserve transmissibility of the virus to a new host. The protein shell accumulates in detectable amounts in cells which are differentiating, not in those which are proliferating or have the potentiality to proliferate.

The usefulness of this concept lies perhaps in the future work that it suggests. Structural attributes that indicate stages in the development of the Shope papilloma virus may be sought with the electron microscope, as has already been accomplished for the viruses of Shope fibroma (23) and Lucké adenocarcinoma (24). Biochemical work with the virus directed toward its purification and fractionation, utilizing the procedures of Beard (29), and leading to bioassay of the nucleic acid and protein moieties, separately and combined, might be undertaken. It is conceivable that tritiated thymidine might be used as a marker, which is incorporated into the DNA-moiety of the virus by biosynthesis, and detected by radio-autography. A histological separation of virus and determination of the infectivity titers for filtrates prepared from the keratinized and nonkeratinized layers of the papillomas must be undertaken. Some of these experiments are now in progress, and their results are awaited with interest, for the concept just outlined would, if true, help resolve some of the long-lasting conflict concerning the roles of intrinsic and extrinsic factors in carcinogenesis. One sees that an incomplete virus would be indistinguishable from an intrinsic factor, until it chanced to declare itself by becoming complete and thenceforth to be identified as extrinsic.

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AMERICAN INSTITUTE OF NUTRITION

Silver Anniversary Symposium[1]

Where Are We Going in Nutrition?

Chairman: C. GLEN KING

OPENING REMARKS BY THE CHAIRMAN

MEMBERSHIP IN THE AMERICAN INSTITUTE OF NUTRITION suggests at once a reasonable degree of interest and competence as a nutrition scientist. However, when one examines the range of subject matter encompassed by the publications of members, it is clear that our experimental work ranges all the way from physics, mathematics and chemistry to genetics, psychology and sociology.

As research scientists, our members explore the frontier of new knowledge. As educators, we attempt to organize, transmit and interpret the most valuable information to others. As citizens, we are obligated to meet, in reasonable degree, the opportunities to make our resources in knowledge, skill and time available in practical services to our fellow men.

In proportion to our response in these basic areas of service, we merit recognition as a profession. Around a central core of interests and skills, specialized areas of professional activity continually expand as a part of our growing cultural pattern.

By its nature, the science of nutrition contributes constantly to the training and intellectual equipment of personnel in several professions. The speakers on this afternoon's program have been selected to orient our present position and to stimulate our imagination as we look ahead from the Silver Anniversary of the Institute in 1958 to the Golden Anniversary in 1983.

[1] Philadelphia, April 16, 1958.

VALUES IN THE AMERICAN INSTITUTE OF NUTRITION: BACKGROUND AND FOREGROUND

ROBERT R. WILLIAMS[1]

Summit, New Jersey

THOSE WHO WERE CONCERNED with the early years of the American Institute of Nutrition are aware that the first Institute was founded in 1928. It was a small select body of twelve members who constituted the Editorial Board of the *Journal of Nutrition*. It was not until 1933 that definite steps were taken to enlarge the American Institute of Nutrition into a more widely representative body. At a meeting on April 10, 1933, under the Chairmanship of Dr. H. C. Sherman, President, 103 new members were elected to the Institute from the Federation membership and 63 additional ones from outside the Federation. Thus the membership leaped in a single day from 11 to 178. In addition, 51 other persons are recorded as being interested in joining but action on their names was deferred. Presumably the Board of Trustees were beginning to experience some mental fatigue as considerable action had been taken earlier in the day to transfer the *Journal of Nutrition* to the Wistar Institute which now owns it.

It appears clear that the purpose of the incorporation of the early American Institute of Nutrition was to provide for the legal ownership and operation of the *Journal of Nutrition* under a set of by-laws filed with the Department of State of New York State. The Board of Trustees had a membership of five and this Board was continued during the first year of expanded membership. This action was taken at a continuation meeting on April 11, 1933, at which time a Committee on Constitution was appointed consisting of L. B. Mendel, Chairman, J. R. Murlin, Paul E. Howe, Icie G. Macy and Mary S. Rose and the membership dues were fixed at $1.00 per year.

In view of the two stages in the organization of the present American Institute of Nutrition, some question may be raised as to whether we are celebrating at this time the 25th Anniversary or the 30th. No change of name was effected at the time of the expansion and it is clear that 1958 is the 30th Anniversary of the original body and the 25th of the larger more representative one which now exists. Each member is entitled to make his own decision.

All will agree, however, that we should honor the names of the original founders by listing them here as they appear in volume 1 of the *Journal of Nutrition*, September 1928. They were: Eugene F. DuBois, Herbert M. Evans, Ernest B. Forbes, Graham Lusk, Elmer V. McCollum, Lafayette B. Mendel, Harold H. Mitchell, John R. Murlin, Mary S. Rose, Henry C. Sherman, and Harry Steenbock. The names of Thorne M. Carpenter and E. P. Cathcart appear later in volume 3, 1930. These persons were the true founders of the American Institute of Nutrition whether one is referring to the small group of 1928 or the larger Institute of 1933.

It will already have become evident that the early background of the Institute was largely centered on the aim of providing a Journal of Nutrition where papers revealing progress in this youthful field of science might be published. This step was very necessary to bring about a general recognition of the birth and viability of the infant. Many of us began life as physiologists or chemists and failed to recognize ourselves as budding nutritionists until we were formally told that there was to be such a thing. Even the term biochemist was then little used in this country—more in England. Biochemistry as then taught was known among students as 'P Chem'. and was chiefly concerned with urine analysis and the preparation from tissues of a few crude mixtures called 'hemoglobin', 'myosin', 'cerebrin' and the like. I still have the 1910 edition of Hawk which I used in college and I still wish I knew everything in it well enough to interpret it in the light of more modern knowledge.

It is quite clear that the Founders of the Institute were motivated by a desire to build a competent science of nutrition out of the rather chaotic mass of fragments of knowledge then in existence. However, we may be sure that they differed widely with one another about what was destined to prove important and how the new science would take shape. There had been sharp

[1] President, American Institute of Nutrition.

controversy over a period of some 20 years over the significance of those vague substances called vitamins and particularly about the propriety of that term. Graham Lusk closed his career with a conviction that the calorimetry of foods was the really important aspect of their utilization. Mendel exhibited small patience with the upstart, Casimir Funk, and administered several sharp rebukes to his alleged disposition to substitute speculation for arduous experiment. McCollum was an ardent advocate of the importance of the minor but essential components of foods though he wanted to name them his way. In short, there would have been no agreement among the Founders in 1933 about what was to prove true except in a very broad way.

With the great advantage of hindsight, we in 1958 can appraise the events in much better perspective. No one today will dispute that the discovery of the vitamins and the gradual elucidation of their chemical constitutions and physiological functions formed a chapter of capital importance in the science of nutrition. The writing of this chapter corresponds almost precisely with the period of the first 25 years of the life of the American Institute of Nutrition. To illustrate this fact, I have prepared a very brief chronology of vitamin discovery. For brevity I have, of course, be forced to omit a vast amount of preliminary observation leading up to these discoveries as well as many important correlated facts as they developed.

CHRONOLOGY OF VITAMINS

Year	*Isolation or Identification*	*Structure or Synthesis*
1925	Vitamin D by irradiation	
1926	Vitamin B_1	
1928	Inositol	
1931	Vitamin A	
1932	Vitamin C	
1933	Riboflavin	Vitamin C
	Pantothenate	
1935	Biotin	Riboflavin
1936	Anti-egg white factor	Vitamin D
	Vitamin E	Thiamine
1937		Vitamin A
		α-tocopherol
1938	Nicotinic identified as pellagra-preventing	*dl*-α-tocopherol
	Pyridoxine	
1939	Vitamin K	Vitamin K
		Pyridoxine
1940	P-Aminobenzoic acid	Alopecia as inositol deficiency
		Pantothenate
1942		Biotin structure
1945	Folic acid	Folic acid
1948	Vitamin B_{12}	Folinic acid
1955–56		Vitamin B_{12} structure

It will be seen that at the time of the founding of the present Institute only 3 vitamins had been isolated and the chemical constitution of none of them was known. We also had inositol, nicotinic acid and choline at that time but no one knew that they had nutritional significance. Within 7 years thereafter we had 10 vitamins which could be produced in pure form synthetically and 5 were in commercial manufacture. Today we have 14 in the category of fully known distinctive substances producible in any desired quantities.

In retrospect all will agree that these discoveries laid the foundations for *a*) our modern concept of enzymes, *b*) some appreciation of the chemistry of vision, *c*) some notion of the chemistry of genetics as well as *d*) a mass of practical knowledge which has found application in the evaluation of human diets and the clinical recognition and treatment of human diseases.

I believe we will all now agree that the great era of vitamin discovery is coming to a close. This obvious fact reconciles all of us, even those who were involved in the exciting adventures of that era, to acknowledge that there is still much we need to know about the major components of foods. Even a quick glance over the nutrition work now in progress reveals major developments now being born concerning protein, carbohydrates and fats—the bulk components of our food supply.

As to proteins, the character of the major problem has become clear, as the early findings of Osborne and Mendel concerning the essential amino acids have ramified into much more detailed knowledge through the work of Rose, his pupils and others. The whole nutrition world is still agonizing, however, over some simple effective method of stating the human needs for proteins so that the non-specialist in protein chemistry can evaluate the shortcomings of human dietaries and guess at what may be practical remedies. The wide prevalence and severity of kwashiorkor has given strong motivation for an early solution.

In the field of carbohydrates, numerous discoveries of surprising specificities in this category

of substances, once supposed to be interchangeable nutritionally, give hints that almost anything can happen. Perhaps the next 25 years will be the era of carbohydrates.

Right now, however, the fats and the lipids are having their day. Ten years ago one might have been forgiven for regarding the fats as a dead field. However, today with the rising appreciation of atherosclerosis and associated heart failure as the focal nutritional disease of the well-fed countries of the West, there is no other equally active field of research. We are still in a state of confusion. No final conclusions are possible but all of us look forward to important developments in the not distant future.

All in all it is clear that we are back dealing with the major components of food rather than the minor ones which loomed so importantly on the horizon of 1933.

In conclusion I wish to say a few words about the present-day civic duty of nutrition scientists. Our world is in a state of political confusion. Civilization is divided into two opposing camps, nearly equal in strength, each camp armed with weapons capable of destroying all that human history has produced. The two camps are vying with one another for the favor and the trust of all the most populous underdeveloped lands of earth. These huge populations are in a ferment of unrest, the major underlying cause of which is food shortage and malnutrition. In the light of these events, the most important duty and function of the American Institute of Nutrition during the next 25 years will be to apply our scientific knowledge to the correction of this great evil. If necessary, further advance of our pure science can wait. That is my sober view.

I do not mean to say that pure science must wait or even that it should wait at the present juncture. It is clearly evident that we need a much fuller understanding of the causes of protein malnutrition and of possible remedies for it than we now possess. We lack considerably of a full knowledge of how kwashiorkor can be attacked most successfully. We are still fumbling toward a complete and precise definition of its cause.

I shall pass over lipid chemistry and malfunction. The precise cause of death from heart failure of many persons in the prime of life, here in the rich Western world, is not likely to be very long neglected.

My primary concern is with the underfed rather than the overfed and this can be justified on the ground that the former greatly outnumber the latter.

We know something about at least 14 vitamins but in respect to their functions in the body, we do not know enough about any of them to appreciate fully their possible roles in the development of a future well-fed world. I shall mention only riboflavin as an example. In humans we recognize ariboflavinosis only as a disease which produces rather trivial sores in the corners of the mouth and may in extreme cases impair the eyes. From our experience with experimental animals we are led to presume that ariboflavinosis has far more serious consequences in humans than we can at present define. Somebody might die of ariboflavinosis and we would not know what struck him down. This is not an idle and academic question, for the military nutrition surveys conducted in the last four years in Formosa, Korea, the Philippines, Pakistan and Iran indicate that ariboflavinosis is very prevalent indeed throughout Asia. If our recommended daily allowances of riboflavin approximate the true needs of humanity we are going to have to scratch for the supplies of riboflavin which will be required. Few Asian foods apart from milk are rich sources of riboflavin and in such a country as Korea where milk, except human milk, is almost unknown to the masses, it is well nigh incredible that milk can be supplied in sufficient quantity within the lifetime of any person here present. Riboflavin from synthetic and fermentation sources is the sole known potential source but the big question is how are we going to get riboflavin into the needy mouths of nearly all Koreans. The problem will not be taken seriously so long as cheilosis is the only sign we can point to.

Problems such as this must not be neglected in favor of researches on the enzymes of neurospora—not if we really mean to save our civilization for the benefit of posterity. The science of nutrition has come of age and it must meet its mature responsibilities. There is very great and urgent need that our foreign aid program should put good nutrition of underprivileged peoples in the forefront of its objectives. The problems are enormous; the remedies few and laborious. The types of better farming which we know in America are applied with difficulty and incredibly slowly under Asian and tropical conditions. The American farmer just could not make a living on the tiny plot of land which the Indian farmer has to till. In common with many other American teachers, many of them more devoted and per-

sistent than I, I started to teach school gardening in Occidental Negros, Philippines, in 1908. The effort has been continued by thousands of teachers through the past 50 years, but it still remains true that home gardening in the Philippines is a rarity. Also it still remains a crying necessity for the supplementation of the Filipino diet. It is high time that American nutritionists should take seriously the task of practical improvement of the feeding of Asians—before we meet these same Asians on the field of battle under Communist banners.

Some endeavor has already been made to persuade our State Department to recognize nutrition as a major concern of our foreign aid program. I wish I could see signs that it will be taken seriously. There are many deterrents to success in this endeavor. *1)* Continuing neglect of nutrition in medical schools is responsible for the fact that many physicians still decry the importance of nutrition. Correction of this neglect was the most frequently cited reason for founding the original American Institute of Nutrition but this objective has by no means been fully attained. *2)* We have still no major success to which we can point in the betterment of the nutrition of any underprivileged people. The job is a tough one and we simply have not put our best minds to it with determination. If Communist China can show, as she claims, a vast betterment of the welfare of the masses under her control, the West will be sunk for we cannot as yet show that sort of results. *3)* The most fertile-minded American nutritionists are still preoccupied largely with their laboratory experiments.

How can we possibly influence our public opinion and our government sufficiently to effect this reform without the unified support of those who know the subject best? If the American Institute of Nutrition should see fit to refuse to subscribe to this cause another organization that will do so will be necessary. Eventually all the members of the present Institute would be caught in the tide, so the Institute will do better to accept the responsibility as its own.

DISCUSSION

W. H. Sebrell, Jr.

From Columbia University, School of Public Health and Administrative Medicine, New York City

Dr. Williams' excellent review of the origin and history of the American Institute of Nutrition has pointed out the important role which the Institute has played during the period of our greatest advance in our knowledge of nutrition. As. Dr. Williams has mentioned, it has been a rather small group of scientists holding an annual scientific meeting and supporting the *Journal of Nutrition*. I think we can anticipate that in the future its role will be even more important and that it will assume new functions.

There are several areas in which the Institute of Nutrition should assume an increasingly important role. Although many members, I am sure, will have differing opinions about the propriety of the Institute doing some of the things which I am going to suggest, they are things to which we should give careful consideration. The Institute should become an effective year-round body so that it can conduct continuing programs. As nutrition research progresses, it becomes more obvious that nutrition is wider in scope and importance than most of us ever vizualized. Every new discovery in the field enlarges the area and emphasizes its importance in health and disease. As we now move into more and more studies of the function of vitamins, more and more studies on the pathology of deficiency diseases, more and more studies on the relationship between malnutrition and degenerative diseases, the importance of the Institute of Nutrition as a scientific body can be expected to become even larger. One very important area is that of public education. We badly need in this country better means of effectively and authoritatively informing lay people about nutrition. It is a subject in which there is a wide interest that is not being adequately met. It is my opinion that at some time the Institute of Nutrition should give some consideration to creating a project on public education.

As the Institute of Nutrition becomes larger and the ramifications of public health and medical aspects of nutrition become clearer, it seems to me that the most important function which the Institute could assume would be that of representing the opinions of nutrition scientists in national and international policies and programs. Scientists these days are expected more and more to take part in the shaping of governmental programs. The Institute of Nutrition, as the most authoritative body in the field, through making public the considered opinions of its members, may in the future assist in developing the policies of this government as they effect the nutrition of the people.

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THE BIOCHEMIST IN NUTRITION

C. A. ELVEHJEM

From the University of Wisconsin, Madison, Wisconsin

THE ASSIGNMENT which I have been given today is a fascinating and challenging one. I am sure that one could spend many months gathering data and information on the relation of biochemistry and nutrition. We would undoubtedly find that progress was most rapid when there was a meeting of minds from these two disciplines. Furthermore proper relationships in the future will accelerate solutions of many of the remaining problems in both fields. Unfortunately, I have not had time to make such a survey and naturally my facts will be meager and most of what I have to say will be based on impressions from very preliminary observations. I believe all of you will agree that we are interested in establishing sound scientific facts and that it makes little difference whether these facts are obtained by physiologists, biochemists, nutritionists or clinicians. It is very satisfying to all of us that we can work together and each contribute his talents to the solution of much larger problems.

Someone recently remarked, "The sordid truth is that the fellowship of educated man has become increasingly to resemble a zoo, with each of us duly labeled chemist or poet, or economist, or what not, blatantly parading his uniqueness in his appropriate cage." These divisions are established for temporary convenience but unfortunately often tend to become permanent or are continued for too long periods of time. Therefore, I hope our distinction between a biochemist and a nutritionist will be used only as long as it adds to our rate of progress.

Just as biochemistry grew out of physiology, so the American Institute of Nutrition was dependent to a large extent on the background of biochemists. It is true that in the field of biochemistry we had the strong influence of workers in agricultural colleges, or so-called agricultural chemists. So our nutritionists had a background in biochemistry closely associated with medical schools or with biochemists who had their background in agricultural chemistry. With this background we had those who leaned more strongly to the chemical aspects of biochemistry in nutrition and others who developed more from the area of clinical medicine.

Undoubtedly the central figure involved in the emergence of nutrition from biochemistry was Lafayette B. Mendel. Dr. Mendel was president of the first scientific session of the American Institute of Nutrition. He had received his introduction to the field of nutrition from Russel H. Chittenden. In the biographical memoir of Dr. Chittenden, Dr. Vickery points out that Chittenden in the early years of his career became interested in the action of enzymes in the processes through which the food passes after ingestion. He goes on to say, "This finally led to the more general field of nutrition and included fundamental investigations that prepared the way for the outstanding work of his successor Mendel." In a paper read by Dr. W. C. Rose at the Third Annual Meeting of the American Institute of Nutrition entitled 'Lafayette Benedict Mendel—An Appreciation' (*J. Nutrition* 11: 607, 1936), Dr. Rose pointed out, "Scarcely any aspect in nutrition escaped his scientific curiosity." Dr. Rose further pointed out that 92 students received the degree of Doctor of Philosophy under the direction of Dr. Mendel. It is interesting that a large proportion of these students later became leaders in the field of nutrition. One need only mention W. C. Rose, H. B. Lewis, A. H. Smith, Icie Macy Hoobler, Harry Deuel and many others, who are recognized as biochemists but who have made very significant contributions in the field of nutrition. All of these received their training under Mendel.

Another very important factor in the close connection between biochemistry and nutrition is the fact that the *Journal of Biological Chemistry* for many years was the important vehicle for the publication of nutrition studies. Again Mendel was undoubtedly responsible for this close relationship, since in 1905 he became one of the collaborators to the editors of the Journal and in 1911 he became one of the editors. In 1933, McCollum was added to the Editorial Board, Rose was added in 1937 and H. B. Lewis in 1938. All of these men were active in the field of nutri-

tion and were interested in seeing properly prepared papers dealing with nutrition accepted for this Journal. A survey of the first 50 volumes of the *Journal of Biological Chemistry* indicates that 97 papers were published on nutrition. Names appearing on these papers include, Osborne and Mendel, McCollum, Hart, Steenbock, Parsons, Sherman, Rose, Geiling, Hogan, Sure and Morgan. In the index to volumes 126–150 (1938–43), which was during the period when the American Institute of Nutrition became a member of the Federation and the *Journal of Nutrition* had been published for a period of 10 years, there were only 7 papers listed under the heading of nutrition. However, this is not necessarily indicative of a large drop in papers dealing with nutrition because papers were now indexed under different headings such as diet, lipids, amino acids, and so on.

In order to be more certain of my facts, I go back to the article by R. H. Chittenden on 'Some Phases of the Growth of Physiological Chemistry in America' (*Yale J. Biol. & Med.* 4: 371, 1932) in which he mentions briefly the development of work in nutrition. He states, "Among the early lines of experimental work on nutrition in this country the studies of Wilbur O. Atwater deserve special notice since he with E. B. Rosa devised the first respiration-calorimeter to be used in America, . . . with this apparatus Atwater and his collaborators, notably Francis G. Benedict, conducted many experiments on the metabolism of matter and energy in the human body. . . . The work thus inaugurated has been carried on ever since by Benedict with many collaborators in the Nutrition Laboratory of the Carnegie Institution of Washington, yielding results of great value for the understanding of many problems of human nutrition." Dr. Benedict became a member of the American Society of Biological Chemists in 1906 and was a charter member of the American Institute of Nutrition. T. M. Carpenter, also with Carnegie Institution, was the seventh president of the American Institute of Nutrition and one of the founding group. Eugene F. DuBois, who continued active work in calorimetry, was the first chairman of the founding group of the American Institute of Nutrition in 1928 and served as the third president of the present American Institute of Nutrition.

Chittenden goes on to speak of the contributions in the field of protein requirements, mentioning the work of Otto Folin, Donald D. Van Slyke and others, who were active in the field of biochemistry but gave little attention to the specific field of nutrition. He then mentions the work of Osborne and Mendel from 1911–1928 as of the greatest value in establishing the close relationship between the chemical constitution of proteins and their biological value in nutrition. This, of course, was followed by the very extensive work of William C. Rose. Finally, he states, "No discovery of recent years in the domain of physiological chemistry has done more to revolutionize views regarding the physiological value of natural food products, and the requirements essential for growth, maintenance and general well-being than the discovery of the vitamins. Dating from about 1911 the volume of work by American investigators has been not only large, but has constituted an extremely valuable contribution to knowledge of the part played by these somewhat intangible substances in the upkeep of the normal nutritional rhythm and the consequent maintenance of bodily health. . . . The work of Osborne and Mendel, Hart and Steenbock, E. V. McCollum, H. C. Sherman, Walter H. Eddy, LeRoy S. Palmer, A. F. Hess, E. A. Park, R. A. Dutcher, H. M. Evans, Goldberger, and Voegtlin is especially noteworthy, though mention of many other workers in this field would be equally justified."

The mention of some of these names brings to mind the diversity of background of these investigators. Some we might call classical biochemists, others had a different background. McCollum had early contacts with Mendel but carried out his work on vitamins in an agricultural college and later transferred to a school of public health. Hart had his early training in analytical chemistry although he had experience in Germany with some of the leading biochemists. He became a member of the American Society of Biological Chemists in 1910 and was one of the charter members of the American Institute of Nutrition. Steenbock had his early experiences in an agricultural college but again had contact with Mendel in the field of nutrition as well as Neuberg in the field of biochemistry. Sherman was trained as a chemist and made a very important contribution to the field of nutrition by emphasizing the quantitative aspects of early vitamin assays. He was the first to use statistical methods to evaluate data on animal growth. Hess, Park and Goldberger were definitely in the field of medicine. Both Drs. Hess and Park were charter members of the American Institute of Nutrition. Palmer and Dutcher also spent most of their activity in the field of agricultural chemistry and were also charter members of the American Institute of

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Nutrition. Evans would probably be classified as a physiologist but was also a charter member and a member of the first Editorial Board of the *Journal of Nutrition* in 1928.

The review by Chittenden gave no consideration to minerals or trace mineral elements in nutrition. At the time his review was written there was little emphasis on trace mineral elements although considerable work had been done on the macro elements. The early work on calcium and phosphorus was carried on to a considerable extent in agricultural colleges, largely, I suppose, because of the importance of these minerals in livestock feeding. Work by Hart, McCollum, Mitchell, Maynard and many others gave a sound background to the importance of these macro elements in nutrition and the biological aspects dealt largely with bone formation. Some of these same workers encountered iodine deficiency in farm animals and, together with the excellent work of such biochemists as E. C. Kendall and Harington, gave iodine a definite place in metabolism. The announcement that copper was essential in nutrition was made through the *Journal of Biological Chemistry* before the American Institute of Nutrition was organized. However it is interesting to note that a number of papers on other trace mineral elements were given an important place on the programs of the Institute during the early days.

When I first started thinking about this paper I thought that I might get valuable information from the issues of the *Journal of Nutrition* including the photograph and short biographical sketches of outstanding workers in the field of nutrition. In checking these issues I was surprised to find that well over half of the individuals included were from foreign countries and that relatively few could be classified as American biochemists. This observation probably indicates two important points. One, that nutrition is an international problem and that many of the early contributions in the field of nutrition were made by foreign workers. Second, since the photograph is only included after the death of an individual it is evident that nutrition is a relatively young science and that many of the workers in this field are still active.

In this connection we might pause a moment to speak more extensively about two of these individuals, Babcock and Hopkins, both of whom were great pioneers in the field of nutrition. I doubt that we could classify Babcock as a biochemist due to the fact that he had the privilege of living before definite categories were established. His motivation was largely the urge to know and it made little difference to him whether he asked himself why bodies fell to the earth at a certain speed or why a piece of beefsteak having the same caloric value as a piece of coal was more nutritious. In the words of E. A. Birge, President of the University of Wisconsin, "His mind continually sought the unexpected, the unknown, he neither formalized his results nor organized great masses of knowledge, nevertheless he became the number one hunger hunter in this country." Hopkins, on the other hand, became the first tenant of the chair of biochemistry, perhaps the first in the world, established by the University of Cambridge in England in 1914. However when Professor Michael Foster invited Hopkins to come to Cambridge in 1898 to develop the chemical side of physiology he commented that he went there without any training as a specialized biochemist. He had never paid an orthodox visit to a German laboratory and indeed he had had no contact with any master of the subject.

One might expect then to find some very interesting information by studying the *Federation Proceedings*' listing of the membership of the American Society of Biological Chemists and the American Institute of Nutrition. It would be interesting to study each name and attempt to determine whether the contributions by this individual were initiated largely from the point of view of nutrition or from the point of view of biochemistry. It would be an enormous task but may I suggest that it would be a very interesting one. Perhaps I can make a few generalizations. First, about 40% of the members of the American Institute of Nutrition are also members of the American Society of Biological Chemists. Of the older members it is obvious that they first became members of the American Society of Biological Chemists and later the American Institute of Nutrition. In the case of some of the younger members the reverse is true. It is also interesting to note that many of the members of the American Society of Biological Chemists are making important contributions in the field of nutrition but have not become members of the Institute. It is also interesting to note that the individuals becoming members of the two societies, roughly in the period of 1930 to 1940, have made important contributions not only in the field of nutrition but in the more biological aspects of the mechanisms involved in the utilization and metabolism of many of our nutrients. May I

mention just a few: R. J. Block, H. E. Carter, L. R. Cerecedo, Paul Day, Vincent duVigneaud, W. H. Griffith, N. B. Guerrant, Paul György, C. G. King, S. Lepkovsky, L. C. Norris, J. M. Orten, J. H. Roe, W. D. Salmon, W. H. Sebrell, F. J. Stare and H. H. Williams.

In other words, this period might be designated as the important period of biochemistry of nutrition. I know that in my own case, with my background in biochemistry and further emphasis on the importance of biochemistry during the year that I spent in Cambridge, England, I was especially interested in the mechanism of action of vitamins which eventually led to the close relationship between vitamin and enzyme. Later, biochemists with an interest in bacteriology made important contributions in bridging the significance between microorganisms and larger animals. To be sure nutrition played a very important role in emphasizing this relationship and was first clearly recognized when some of the nutrients, especially vitamins, were shown to be universally needed by all living cells. Later the biochemists clearly demonstrated that most of the metabolic processes, at least the core processes, are practically identical in all forms of living matter. Today when most of the essential nutrients have been identified and characterized, we are undoubtedly reaching a period when we will see a differentiation between the two fields. At present the emphasis is on enzymes and metabolic pathways but there are still important relationships to study, especially between nutrients and balance between nutrients.

DISCUSSION

ALBERT L. LEHNINGER

From the Johns Hopkins School of Medicine, Baltimore, Maryland

AS A BIOCHEMIST I am very glad to have the opportunity to make some comments on Dr. Elvehjem's paper on the relationship of biochemistry and nutrition. Although my own work deals with the enzymatic organization of the mitochondria in relation to their function in respiration and phosphorylation, it has been rather impressive how often developments in the science of nutrition have affected the course of biochemical investigations in this area. One of my first lessons on this relationship actually came from our speaker. It was Dr. Elvehjem himself who was responsible for calling my personal attention to some relationships between nutrition and enzymology pertinent to some research I once carried out on the mechanism of fatty acid oxidation. This incident occurred at a very crucial and significant time in my own training as a biochemist, namely, on a hot June morning some years ago, while I was defending my Ph.D. dissertation on the mechanism of fatty acid oxidation before an examining group of distinguished biochemists of the University of Wisconsin. After I had somewhat proudly presented this hypothesis, Dr. Elvehjem asked me if my theory of fatty acid oxidation was compatible with the fact that rats on a diet deficient in thiamine do not show deficiency symptoms when changed from a diet rich in carbohydrate to a diet rich in lipid. I can only report that this fact, which I had not been aware of until then, thoroughly deflated my hypothesis. Actually, to my knowledge, the biochemical basis of this nutritional fact is still not yet adequately explained, and it is typical of a number of rather intriguing nutritional phenomena having a very important bearing on the more purely biochemical and enzymatic aspects of intermediary metabolism. It is of some interest that considerable attention at these Federation meetings will be focused on the possible coenzyme role of tocopherol and vitamin K in biological oxidation and phosphorylation.

Dr. Elvehjem has covered such a broad sweep of the history of the relationships between biochemistry and nutrition, as has Dr. Williams, that I can add but little more in the line of general discussion. It appears to me, in keeping with the current developments in biology and medical sciences in which interdisciplinary barriers are breaking down so rapidly, that it will be very difficult and really undesirable in the future to dissociate nutrition from biochemistry in any categorical way. I would expect that each of these fields is likely to continue to make a large impact on the other, such as is happening currently in the field of the relationship between lipid nutrition and the biochemistry of fat transport in the blood. Perhaps with a fuller understanding of the biochemical mechanisms involved in the function of various essential nutrients, it may be possible to help dispel the irrational food 'faddism' and popular mythology too often associated with human nutrition. In any case there seems every reason to expect that the next 25 years will see at least as much progress in nutritional science as this 25th anniversary celebrates today.

NUTRITION IN MEDICINE

GRACE A. GOLDSMITH

From Tulane University School of Medicine, New Orleans, Louisiana

ON THE SILVER ANNIVERSARY of the American Institute of Nutrition, it is pertinent to look back and consider what nutrition meant in medicine a quarter of a century ago before discussing recent advances in knowledge or attempting to prophesy as to the future. In 1933, medical text books contained short chapters on the deficiency diseases, brief discussions of obesity and descriptions of therapeutic diets for use in a number of pathologic states (1, 2). It was recognized that the diet should furnish fluid, protein, including the essential amino acids, the mineral elements iodine, calcium, phosphorus, sodium and iron and vitamins A, B, C, D and B_2 or G. Beriberi, scurvy and rickets were recognized as diseases due to vitamin deficiency and the clinical features of these conditions were well known, having been described many years or even centuries earlier. Vitamin A deficiency had been shown to be responsible for xerophthalmia and probably also for night blindness. Pellagra was considered by most authorities to be due to a deficiency of an unknown dietary factor, probably a vitamin, but the toxic and infectious theories of etiology had not been abandoned completely. The pathologic changes in the deficiency diseases had been studied in considerable detail but there was little information to explain the changes observed. Diagnosis of deficiency was dependent on clinical manifestations and the only laboratory procedures available were X-ray examination of the bones for detection of scurvy and rickets, and the electrocardiogram, which showed non-specific abnormalities in beriberi. Treatment of vitamin deficiencies was dependent solely on diet since vitamins had not been isolated in pure form except for vitamin D, which was available as irradiated ergosterol, and vitamin C which had recently been identified as 'hexuronic acid' (3). Brewer's yeast had been found to be valuable in the management of pellagra and was widely used throughout the southern United States as a preventive measure. Sprue was a disease of unknown etiology that was treated with a high protein, low fat, low carbohydrate diet. Liver had been found to be effective in the treatment of pernicious anemia and a crude extract of liver had been prepared. Castle had proposed a theory of the etiology of pernicious anemia, namely, that an 'intrinsic' factor normally found in the gastric juice was lacking in patients with this disease. He postulated that this 'intrinsic' factor combined with an 'extrinsic' factor in food to form the anti-pernicious anemia substance of liver.

Little was known about nutritional requirements except for calories and protein and almost no information was at hand as to the metabolic function of essential dietary constituents. In the therapy of non-nutritional diseases, considerable emphasis was given to special diets but in most instances attention was directed to calories, bulk and consistency, frequency of feedings and omission of 'irritating' foods rather than to the quality or nutrient content of the diet. Parenteral feeding was used only rarely and was limited to administration of glucose, normal saline, sodium bicarbonate and Hartman's solution. Transfusion of whole blood was a major procedure used only in extreme emergencies and plasma was not available.

In the past 25 years, the remarkable advances in nutritional biochemistry have contributed extensively to knowledge of nutrition in medicine. In the first part of this period, thiamine was isolated and its chemical structure determined (4). Riboflavin was found to be a constituent of the vitamin B complex and the signs associated with deficiency of this vitamin were described. (5) Niacin was found to be the pellagra-preventive factor (6), and, somewhat later, the amino acid tryptophan was found to be a precursor of niacin (7) and the pathway of conversion of tryptophan to niacin was delineated. (8) Extensive investigation led to isolation and chemical characterization of other vitamins of the B complex: folic acid, pyridoxine, pantothenic acid, biotin and vitamin B_{12}. (9) Vitamin K was discovered and the structure of vitamin E determined (9).

As a result of numerous studies, the role of the various vitamins in intermediate metabolism has been gradually elucidated and the function of many of these factors as coenzymes has been

established. These biochemical investigations were accompanied by studies in animals and in man resulting in estimation of requirements for many nutrients and delineation of the syndromes associated with deficiency of most of these substances. Deficiency of vitamin A (10), ascorbic acid (11), thiamine (12), riboflavin (13), niacin-tryptophan (14), pyridoxine (15), biotin (16) and pantothenic acid (17) were induced in human subjects and the human requirements for most of these factors determined. Discovery that vitamin B_{12} was the anti-pernicious anemia factor of liver was one of the outstanding accomplishments of recent years (18, 19). Subsequent studies of vitamin B_{12} and folic acid have partially clarified the role of these factors in the macrocytic anemias and permitted more accurate diagnosis and more effective therapy. The role of minerals in metabolism has been widely investigated and the need for many of these elements estimated; at least fourteen are now known to be essential dietary constituents for man (9).

Recently, much attention has been directed to protein nutrition. The human requirements for the essential amino acids have been determined in adults (20, 21) and in infants (22). The prevalence and seriousness of protein malnutrition as a world health problem have been recognized. An important syndrome of protein malnutrition that occurs in infants and children, kwashiorkor, has been characterized and is under extensive study on an international scale (23, 24). The importance of protein deficiency in the pathogenesis of chronic liver disease has been recognized and the role of nutrition in the prevention and therapy of cirrhosis has received considerable attention (25).

It is now known that protein deficiency is a common complication of many pathologic states. Loss of protein occurs in renal diseases particularly in the nephroses, in effusions into serous cavities, from wounds, burns and exudates and following physical or operative trauma. Protein needs are increased in hypermetabolic states. Therapy of these conditions has become much more effective since protein concentrates, human serum albumin and protein hydrolysates suitable for intravenous administration have become available.

The roles of individual amino acids in metabolism are beginning to be uncovered. The function of methyl groups and of sulfur containing amino acids is being clarified. Studies of diseases due to inborn errors of metabolism, such as phenylpyruvic oligophrenia, have given insight into the function of the involved amino acids and appropriate methods of therapy are being developed (26). Investigation of the conversion of tryptophan to niacin has indicated a coenzyme role for pyridoxine and has provided a useful test for evaluation of the adequacy of vitamin B_6 nutrition (27). These findings and others of similar nature illustrate the close interrelationship among vitamins and amino acids in metabolic processes.

Studies conducted during World War II in prison camps and war-torn countries, as well as controlled experiments in human volunteers, have enhanced our understanding of the pathologic changes which occur in starvation and severe caloric undernutrition (28). Production of experimental obesity in animals (29) has stimulated renewed interest in caloric overnutrition and the pathogenesis of obesity in man. The metabolism of obese persons is being scrutinized and more information sought as to the physiologic mechanisms which regulate food intake. There has been renewed interest in determination of energy expenditure in various physical activities.

Knowledge of human nutrient requirements has advanced sufficiently to permit promulgation of dietary standards and recommended nutrient allowances by several countries and international agencies (30–33). These guides are being used in planning adequate diets for individuals and population groups. The influence of physiologic stress and of disease on nutrient requirements has been the subject of investigation in a number of laboratories. Although much remains to be learned, sufficient information is at hand to plan rational nutrient therapy in many diseases which are not primarily of nutritional origin, but which significantly influence nutritional state. As an illustration, recognition of potassium depletion in diabetic acidosis, in diarrheal states and in a number of stress situations has resulted in the saving of many lives (34). Increased knowledge of the mechanisms controlling the sodium and water content of the body has led to better management of edematous states. The value of diets low in sodium in the therapy of congestive heart failure and hypertension has been amply demonstrated.

Nutritional diagnosis has become more precise. Recent studies in nutritional anthropometry have been of assistance (35), clinical manifestations of malnutrition have been described in considerable detail and numerous biochemical procedures have been developed for evaluation of nutritional status (36). It is now possible to measure the concentration of amino acids, sugars, lipids, vitamins and minerals in blood, urine, other

excretory products and bodily tissues. Tests have been developed which can detect tissue depletion, biochemical abnormalities and disturbances in function of a number of nutrients before clinical signs of deficiency are observed. Measurement of the concentration of enzymes in blood and tissues has been applied in clinical medicine and found useful in diagnosing and following the progress of a number of diseases.

The availability of isotopes and the possibility of labeling nutrients with radioactive elements has made it possible to trace the fate of essential dietary factors from ingestion through metabolic pathways to excretion. Such labeled compounds have proved of practical value in medical diagnosis as well as contributing greatly to understanding of physiologic and pathologic processes. For example, the use of Co^{60} labeled vitamin B_{12} has provided tests for the diagnosis of pernicious anemia (37) and markedly increased knowledge of the pathogenesis of this disease. Another case in point is the important information that has been uncovered in protein metabolism through the use of tracer techniques, including the concept of the dynamic state of body constituents (38). Recently, fat and fatty acids labeled with I^{131} have been used in studying fat absorption (39).

The remarkable advances in the science of nutrition in the past 25 years have changed the whole concept of nutrition as applied to medicine. Nutrition is no longer considered solely in terms of deficiency disease and dietary therapy. Current information is sufficient to allow almost complete eradication of the deficiency diseases but they will remain a problem in many areas of the world until education, technology and an improved economic situation can implement practical application of this information.

Today, nutrition is recognized as permeating all fields of medicine. Medical nutrition includes knowledge of the metabolic role of nutrients in health and in disease and application of this knowledge in diagnosis and therapy. Attention is directed to biochemical and physiologic function not only in the body as a whole but at the cellular and, perhaps one might say, at the 'sub-cellular' level. The clinician is interested in diagnostic methods and procedures which will assist in evaluation of nutritional status and which will detect abnormalities of function which may be of nutritional import. Provision of adequate nutrition is recognized as of prime importance during pregnancy, throughout the period of growth, for the maintenance of health in adult life and in the prevention and treatment of disease, including diseases of non-nutritional origin. The importance of adequate nutrition in the preoperative and postoperative care of surgical patients has received increased recognition. It is now possible to maintain patients for prolonged periods of time by parenteral feeding. Preparations furnishing amino acids, vitamins, minerals and even fat are available for intravenous use.

The teaching of nutrition has received increased emphasis in many medical schools but there is need for expansion of nutrition education in others. Evidence of a growing awareness of the importance of nutrition is attested by topics discussed in current programs of medical meetings and medical publications. Much of this interest has been aroused by recent investigations which implicate dietary fats and lipid metabolism in the development of atherosclerosis and its complications, coronary and cerebral thrombosis (40, 41).

This brings us to the consideration of the possible direction of future research in nutrition as related to medicine. There seems little doubt that attention will be directed to the role of nutrition in diseases which have not been considered to be primarily nutritional in origin, in particular to the so-called degenerative diseases which occur with increased frequency as age advances. Intensive investigation is under way at present relative to possible etiologic relationships between dietary fats, serum lipids and atherosclerosis. The current interest in lipid metabolism should solve many unknowns including the essentiality of polyunsaturated fatty acids for man and their role in metabolism and the desirable fat content of human diets from both a quantitative and qualitative standpoint. It seems likely that dietary factors other than fat will be found to be implicated in the pathogenesis of atherosclerosis and its complications. Studies in animals suggest that certain amino acids, vitamins and minerals may be involved. In addition, non-dietary factors have been shown to be of importance in the development of degenerative vascular disease.

Problems of obesity will certainly occupy the attention of medical nutrition scientists. Increased knowledge of mechanisms which lead to excessive food consumption and of the metabolism of obese persons should assist in planning more effective approaches to therapy. The relationship of excessive accumulations of body fat to the apparent increase in the incidence of certain diseases in obese persons should be clarified.

The use of radioactive isotopes undoubtedly

will greatly increase knowledge of intermediary metabolism not only in health but in many pathologic states. It is anticipated that many procedures using such isotopes will be developed which will increase the accuracy of nutritional diagnosis. The development of numerous other biophysical and biochemical techniques should contribute significantly to precise delineation of nutritional abnormalities.

Exploration of interrelationships among nutrients will presumably be an important field of investigation. The information thus obtained will probably explain many poorly understood pathologic changes of disease. A proper balance of amino acids in the diet has been shown to be of importance in animal nutrition. It seems likely that this will be found true in man as well. Many vitamin, mineral and amino acid interrelationships have been demonstrated thus far and many more may be uncovered and found to be highly significant. The function of individual amino acids in metabolism will be elucidated. It may be that certain human diseases of unknown etiology will be found to be due to inherited metabolic abnormalities involving amino acids or other nutrients.

Studies with analogues of various nutrients, particularly of those which act as anti-metabolites, have provided information as to the metabolic role of nutrients and their chemical derivatives. These investigations have resulted in the development of compounds which are effective in the therapy of disease. Perhaps the most outstanding example is the use of folic acid antagonists in the treatment of certain types of leukemia (42). Future investigations in this area should increase knowledge of nutrient function and add to the physician's therapeutic armamentarium.

Relationships of nutrition to carcinogenesis have received considerable attention. In experimental animals, the caloric and fat content of the diet has been found to influence the incidence of certain spontaneous and induced tumors (43). Riboflavin has been shown to exert a protective effect on the incidence of azo dye-induced hepatomas in rats. In man, the high incidence of primary carcinoma of the liver in areas where protein malnutrition and cirrhosis of the liver are common is of interest. Recently, it has been found that malignant carcinoids of the bowel contain serotonin (5-hydroxytryptamine) and that serotonin can arise *in vivo* from tryptophan (44). Patients with these tumors excrete increased amounts of serotonin and 5-hydroxyindolacetic acid in the urine. An increase in excretion of these metabolites has also been found in persons with certain other malignant tumors. It seems likely that future research will uncover other metabolic abnormalities associated with malignant neoplasia. Such findings will assist in diagnosis and may be of therapeutic import. If the nutritive requirements of malignant cells differ from normal or if the metabolism of nutrients is abnormal in these cells, therapeutic potentialities involving nutrition become evident.

From this brief review, it is obvious that knowledge of nutrition as related to medicine has increased tremendously in the past 25 years. Advances in this field have been greater than in any previous comparable period of time. Increased interest in research in medical nutrition, expanding research facilities and the availability of an increasing number of trained personnel should lead to even greater accomplishments in the next quarter of a century. In view of current developments, it is anticipated that nutrition will occupy a more important place in medical education in the future than it has in the past.

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DISCUSSION

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Even clinical nutrition is based to a very large extent on animal experiments. Conclusions gained in such animal experiments have proved to be applicable with a high 'batting average' to equivalent conditions in human pathology. As a matter of fact, confirmation by experimentation on animals puts clinical observations often on a much more respected and generally acceptable foundation. Animal experiments may be better supervised, organized and controlled than analogous clinical investigations; thus they permit a more exact, almost mathematical evaluation in contrast to clinical studies with all their inherent difficulties.

For a pediatrician and nutritionist, it is difficult to cite animal experiments in support of the nutritional value of human milk, which in itself is the physiologic food for the young human infant (anything else, including various cow's milk formulae, being considered only substitutes). Human milk is not only not beneficial, but is harmful for all animals used in routine nutritional studies. It is a distinct omission of nutritional research over the last 25, even 50 years, not to pay more attention to human milk as *the* natural, basic food of the young human infant.

Clinical observations taught us to appreciate

at least two specific qualities of human milk given to young infants, i.e. *a*) increased natural resistance to disease and *b*) the unusually homogeneous intestinal flora, with the prevalence of *Lactobacillus bifidus*.

Natural resistance and nutritional factors controlling or at least modifying it are at present in the forefront of clinical interest, with special reference to the increasingly threatening problem of staphylococcal infection. The study of feeding of infants with human milk is in this direction of paramount importance.

The particular role attached to the intestinal flora as perhaps the most decisive symbiotic environmental factor in the life of any living mammalian organism, including man, should receive in the future special attention. This problem is closely related to the problem of 'germ-free life,' experimentally obviously best studied on 'germ-free' animals (chicks, rats, mice and other mammals).

Nutritional research in medicine should give priority to the study of late effects of nutritional errors. In the past the late effects of faulty nutrition experienced in early life have been largely ignored or not taken in due consideration. That such effects may become apparent in late life has been best demonstrated by the studies of Best and his associates on the effect of early choline deficiency of rats in adult life, with the statistically significant high incidence of hypertension and nephrosclerosis in rats that received (in the post-weaning period for a very short time and then intermittently) a choline-deficient diet.

In the future such integration over a prolonged period of time, beginning with infancy and extending to adult life, will become an intriguing and important task, when related to nutrition in early life. A new horizon will open by such longitudinal studies, which may reflect on the etiology and pathogenesis of late degenerative disorders, such as atherosclerosis, hypertension, arthritis, etc., the foundation of all these diseases being perhaps laid in early life.

NUTRITION AND PUBLIC HEALTH

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ABOUT A YEAR and a half ago, in October 1956, a distinguished group of individuals interested in public health met in Arden House as a special task force of the American Public Health Association. This task force was convened for the "specific purpose of translating the interest of the membership into substantive statements which could be used as guides in the future direction of public health and of the APHA."

I believe that the declaration of principles of this task force is of importance to our own Institute of Nutrition in considering the subject which today has been assigned to me for discussion, 'Nutrition and Public Health.' This declaration is as follows: *1*) The goal of public health is the achievement of the physical, mental and social well-being of all the people. *2*) Many professions and groups, as well as a great variety of social and economic forces, including the individual's responsibility for his own health, contribute to the attainment of this goal. *3*) Public health practice is the application of medical, social and allied disciplines in an organized community activity designed primarily to protect and advance the health of the people. *4*) The nature and scope of public health practice are not static, but must change with the needs and desires of the people and with progress in science and technology. *5*) All peoples and nations are interrelated and interdependent in the advancement of public health.

If you agree with these principles our goal then is optimum nutrition for health of all the people. This is a high goal, to be sure, and requires a vast increase in knowledge as well as the application in dietary practices of information now at our disposal and new knowledge as it accrues. Nevertheless, I believe that it is possible on this, our Silver Anniversary, to point to some signal successes in what must be a continuing effort. Almost concomitantly with these successes has come an enlarged horizon and further insight into the importance of nutrition to the continued well-being of individuals and population groups.

DEFICIENCY DISEASES IN THE UNITED STATES

The fight against dietary deficiencies diseases is well known to all. Nevertheless, it may be well at this time to recall briefly where we were a few short decades ago in contrast to where we are today. Two areas—endemic goiter and pellagra—will serve as illustrations.

Before 1924, there were large goiter belts in the United States, where endemic goiter was rampant. This was despite the fact that in the first half of the nineteenth century the favorable effect of iodide on goiter had been demonstrated medically, the inverse relationship between goiter and the concentration of iodine in soil and water in certain regions of France had been shown, and the suggestion had even been made in 1831 that iodized salt be used for the abatement of goiter. In the present century, the year 1918 constitutes a landmark, for in that year was published the classic study by Kimball and Marine of the effect of small amounts of potassium iodide in lowering the incidence of goiter in school children in Akron, Ohio. This was followed six years later by effective public health measures in one state, Michigan. The salt manufacturers agreed to prepare an iodized salt and the Wholesale Grocers' Association agreed to handle only iodized salt for table use in Michigan. In 1924 the results of an extensive survey of Michigan school children placed the incidence of goiter at 38.6%. By 1928, the incidence had decreased to 9%. In 1952, an extensive survey of school children in the same Michigan counties where the 1924 survey had been conducted showed that the incidence of goiter had dropped to 1.4%.

This, to me, represents one of the most dramatic chapters in the story of the fight against deficiency diseases in the United States. Much credit must be given to Dr. Kimball not merely for his part in the demonstration of the effectiveness of potassium iodide but for his patience and persistence in bringing about the translation of this finding into effective public health measures for the widespread control of goiter.

Two other very important public health measures in nutrition were the addition of vitamin D to milk and of vitamin A to margarine. Because of the limited time at my disposal, however, I shall pass over these developments with only this brief mention and use pellagra as the

subject of my second example of successful battles against deficiency diseases in the United States.

In 1928, 30 years ago, pellagra was endemic in this country, restricted largely to be sure to the Southern States. The number of cases in the United States is estimated to have reached 200,000 and for 1928 the number of reported deaths was over 7,000, or some 6 per 100,000 in the total population. Even in 1937, the year niacin was identified as the pellagra-preventive vitamin, the death rate from pellagra was almost half that level, approximately 2.5 per 100,000 total population. The addition of niacin to foods was started in 1941. By 1943 pellagra mortality had decreased to 1 and by 1950 to 0.2 per 100,000 total population. Today, as you know, the incidence of pellagra in this country is very low indeed and deaths from this cause are practically nonexistent.

The reasons for this dramatic change in the status of pellagra in this country—from a serious public health problem to a minor one and from 7,000 deaths yearly from this disease to virtually zero—are undoubtedly complex. Nevertheless, one specific public health measure—the enrichment of corn meal and of wheat flour and white bread with niacin—has undoubtedly played an important part.

Prior to 1943, enrichment was on a voluntary basis. At the beginning of that year, nevertheless, about three-fourths of all bakers' white bread and almost all family flour was being enriched not only with niacin but with thiamine, riboflavin and iron as well. A war food order issued in January 1943 required enrichment of all bakers' white bread. This order was effective until October 1946 and this enrichment program was accompanied by a well-planned education campaign, a national school lunch program, an industrial in-plant feeding program and other measures. Since 1946, enrichment of flour and bread has not been required by Federal legislation but more than half the States have passed laws making enrichment mandatory. In the remaining States, where enrichment is voluntary rather than mandatory, it is nevertheless very widely practiced.

This, too, constitutes to me a most dramatic illustration of how important public health measures in nutrition can be effectuated and how important they may be in benefiting the health of our citizens. Again, I should like to pay tribute to the men who played the key roles in research on pellagra and in translating scientific progress into successful public health programs.

Our country today is essentially free of frank deficiency diseases. In the 1930's a Department of Agriculture survey indicated that the diets of one-third of our people had to be classed as 'poor' while a similar survey in 1955 showed that not more than 10% of diets, judged by the same criteria, would be placed in the 'poor' category. The margin of safety for some nutrients remains small, however, and the situation could change rapidly in the event of a widespread serious depression or in other national emergencies. Neglect at this juncture of the public health measures which insure adequate nutrition would be shortsighted indeed.

Perhaps the necessity for continued attention to public health nutrition measures is in no area better illustrated than in the field of iodine-deficiency goiter. Dr. Kimball has reported that in Calumet, Michigan, during the depression of the 1930's non-iodized bag salt was supplied to families on relief. As a result, while the children of families using iodized salt showed a 3% incidence of goiter, 60% of the children in the families receiving the non-iodized salt exhibited this condition. Further, there have been a number of studies in recent years indicating that our present programs of education and voluntary iodization of salt have not resulted in the eradication of visible goiters. It cannot be shown, to be sure, that all cases of simple goiter are due to iodine deficiency. A recent study in Ohio indicated, however, that the incidence of goiter in children not using iodized salt was almost double that for children regularly using iodized salt—6.1% against 3.4%.

Our sister country to the north, Canada, adopted compulsory iodization of table salt in 1949. It would be of great interest to compare the goiter problem in matched population groups in the goiter belts of the two countries. Such a study should give us much-needed additional information on the extent and urgency of the iodine-deficiency problem in this country today.

In view of the fact that any relaxation in the application of sound public health nutrition practices may result at any time in the reoccurrence of manifestations of one deficiency disease or another in considerable segments of our population, complacency on our part is far from warranted. We are much concerned today with nutrition problems other than those involved in frank deficiency diseases. We should recognize, however, that these new areas of responsibility are additive rather than substitutive and that our

concern with possibilities of dietary deficiencies in this country must remain active.

WORLD PROBLEMS

The enviable position of the population of the United States in regard to the absence of frank deficiency diseases is not shared by numerous other areas of the world. As all of you are aware, many large population groups suffer from a serious caloric deficit and from a severe deficiency of protein, particularly animal protein, as well as from specific vitamin and mineral deficiencies.

Two important activities of recent years, designed to ameliorate some aspects of the world nutrition situation, are the enrichment of rice in the Philippines, under the auspices of the Williams-Waterman Fund, and the program of the United Nations International Childrens Emergency Fund (UNICEF) for the development of practical substitutes for milk for child feeding in underdeveloped countries.

In addition, many of you are familiar with the work of the Interdepartmental Committee on Nutrition for National Defense. The interested agencies are the Departments of Defense, State, Agriculture, and Health, Education and Welfare and the International Cooperation Administration. The purpose of the nutrition program which has been developed by this Interdepartmental Committee is to assist the developing countries of Asia, Africa and South America in improving the health of their people. On request for assistance from a country under the Mutual Defense Assistance program, the ICNND organizes a nutrition team composed of specialists in the fields of medicine, nutrition, sanitation, food technology and agriculture. Surveys have been conducted in Korea, Iran, Pakistan, the Philippines, Turkey and Libya. Recently a nutrition team under ICNND has completed a survey in Alaska, also.

An interesting program now being carried out on the Interdepartmental Committee's recommendation, following a survey by a U. S. Army nutrition team, is the enrichment of rice in Formosa. By this means the daily requirements of thiamine, riboflavin, niacin and iron will be provided at a cost, including the mills and enrichment mixture, of less than one-tenth of one cent per person per day. Initially rice will be distributed to the Formosan Army only but approximately one-fifth of it, it is estimated, will reach the civilian population since Formosan troops use rice in barter to obtain vegetables.

As another concrete example of accomplishments from the ICNND surveys and the recommendations arising from them, I should like to mention the findings of two surveys carried out in Korea. A vast improvement in the nutritional health of the troops occurred between 1953, the time of the first survey, and 1956, the time of the resurvey. It seems certain that an important part of this improvement resulted from the implementation of recommendations made by the 1953 nutrition team. The work of the nutrition teams, collaborating as they do with counterpart personnel in the countries visited, appears to be resulting in improvements of lasting value to the nutritional health not only of the troops but to some extent of the civilian populations as well. It results also in continuing good will as evidenced by the establishment of an annual nutrition conference at the request of Iran and Pakistan. The first such conference was held last year in Tehran and the second is occurring this week in Istanbul and Ankara.

A by-product of these nutrition surveys appears to this observer to be a renaissance of active interest in human nutrition in this country and a heartening increase in the number of individuals skilled in this field.

I should like to submit for your consideration the thesis that not only must the nutrition program of the Interdepartmental Committee be continued but that also through one agency or another, or more properly through the cooperation of several agencies, there should be instituted similar studies aimed more directly at the civilian populations of the so-called 'underdeveloped' countries. Such a program, designed to assist these countries in developing and using their own resources, might have tremendous lasting value to the peoples of these countries and, as a small but important by-product, expand the good work started by the Interdepartmental Committee of giving experience in human nutrition studies to specialists in the United States.

OBESITY: CHRONIC DISEASES

In the United States today, the striking decrease in the incidence of frank deficiency diseases has not left us free of urgent nutritional problems. On the contrary, our horizon has broadened and perhaps for the first time we are becoming fully aware of the potentialities of the science of nutrition.

Obesity has often been stated to be the gravest sign of malnutrition in the United States today. It is associated with a high morbidity experience and a high mortality rate from a wide range of

diseases such as diabetes, liver cirrhosis, cardiovascular-renal disease and many others. Public health measures for the correction of this condition leave much to be desired. 'Group therapy' techniques have been attempted but the long-range results have been rather disappointing. On what appear to be sound grounds increased emphasis is being given to the prevention rather than the correction of overweight. It seems clear that any solution of lasting value will involve the inculcation of better eating habits in the population as a whole and this is obviously a complex and difficult task. A broad and determined attack on this public health problem is urgently needed.

No consideration of malnutrition and public health would be complete or even adequate today without mention of the currently most active field of nutrition research—and an important one certainly—atherosclerosis. A review of the published literature in the field, however, would be time-consuming and inappropriate in this brief review and would undoubtedly be out-of-date as well. I shall leave this subject, therefore, to active workers in the field who are presenting the results of their most recent studies in other sessions of this meeting of the Federated Societies.

Other chronic diseases where nutrition is known to be important include tuberculosis, where undernutrition is known to increase the incidence and severity, and a number of others such as gout, degenerative arthritis and diabetes, where the incidence is greater in those who are overweight.

A defect of great prevalence to which I should like to devote a few moments is dental caries. As all of you are aware, fluoridation of public water supplies is most effective in reducing dental decay. This public health measure is gaining ground although not without encountering resistance on the part of well-meaning but misinformed individuals. Fluorides in the desired concentrations often occur naturally in water used for drinking to the benefit of those using this water. It would seem a logical public health measure, therefore, to add such a naturally-occurring substance which has been shown to be not only harmless but beneficial to water which lacks it. Even were we able today as a public health measure, however, to bring fluoridated water to every individual in the United States, the problem of dental caries would still be with us, although in a greatly reduced degree. More dietary studies are needed. The survey just completed in Alaska by the ICNND, to which I have alluded, is obtaining some very interesting comparisons, in regard to the incidence and severity of dental caries, between those Eskimos who have remained on the native diets and those who have changed to diets containing refined foods.

FAMILIAL OR HEREDITARY DISEASES

Lastly, I should like to touch briefly on a group of diseases which only recently are being recognized as constituting or involving a problem in nutrition. These are the familial or hereditary conditions sometimes referred to as 'molecular' diseases such as galactosemia, phenylpyruvic oligophrenia, mucoviscidosis or pancreatic fibrosis, etc.

Galactosemia has been shown by Kalckar and associates to be due to the absence in afflicted infants of a single enzyme and have devised a simple test for the presence of the disease. If galactose, ingested by the infant as lactose in milk, is not excluded from the diet of those suffering from galactosemia, blindness, imbecility and usually death result. As far as is known, if milk is excluded from the diet development of the child is entirely normal. There is some evidence that as the child grows older another enzyme system for metabolizing galactose comes increasingly into play so that rigid exclusion of milk from the diet throughout the galactosemic's entire life may be necessary. Galactosemia is believed to be a rather rare disease but because of the difficulty of diagnosis, incidence figures are not entirely reliable.

Another disease requiring exclusion or reduction of specific dietary ingredients is phenylpyruvic oligophrenia, another familial disease leading to mental retardation. Encouraging results have been reported from the use of diets low in phenylalanine tyrosine and tryptophane.

A third familial disease and one with a much higher incidence is mucoviscidosis or pancreatic fibrosis. Incidence figures range from 1 in 100 to 1 in 1000 live births. Due to decreased secretion of pancreatic enzymes, digestion is impaired and at one time children with this disease were usually severely emaciated. The feeding of inordinate quantities of food and the provision of pancreatic enzyme preparations corrects to a large extent the starvation aspects of the disease although it does not prevent the fatal outcome.

A fourth familial disease, alcaptonuria, begins with mild manifestations but in middle age serious complications including arthritis and arteriosclerosis often develop. Again, as in galactosemia and phenylpyruvic oligophrenia, the metabolic

defect is the congenital absence of a single enzyme, needed in this case for the metabolism of phenylalanine and tyrosine. In this disease, benefits of special diets have not been demonstrated. By analogy it does not appear improbable that benefit would accrue from a dietary limitation of phenylalanine and tyrosine were this practical for the long periods of time involved.

Galactosemia and phenylpyruvic oligophrenia particularly appear to constitute areas of public health nutrition concern, each with its own individual problems to be solved. The metabolic research activities necessary to the precise definition of such congenital abnormalities as these and necessary for the development of simple and precise diagnostic tests are progressing rapidly and it would not be unexpected if other familial diseases were later added to this list.

In summary and conclusion then:

First. Dietary deficiency diseases have largely disappeared from this country. This is due in part to large-scale public health measures such as iodization of salt, fortification of milk with vitamin D and margarine with vitamin A, enrichment of corn meal with niacin and enrichment of flour and bread with thiamine, niacin, riboflavin and iron.

Second. Despite the virtual disappearance of frank deficiency disease in this country, the margin of safety is not large. Complacency is not justified. We should not feel that newer nutritional problems of public health importance have been substituted for deficiency disease but rather that they have been added to our field of responsibility.

Third. In many parts of the world deficiencies, particularly of calories and protein but also of vitamins and minerals, remain as an extremely important public health problem. This constitutes an important challenge to us as well as to the citizens of the countries directly involved. In addition, it presents an opportunity for training of nutrition personnel.

Fourth. Obesity is one of the most important public health problems in this country today. Our attack on this problem leaves much to be desired.

Fifth. The chronic diseases are widely recognized, not only as public health problems of tremendous and increasing importance but also as related in various ways to nutrition. Atherosclerosis is rightly occupying a great deal of our attention today. In relation to many other chronic diseases there are also important nutrition problems deserving attention.

Sixth. Lastly, there is another important group of diseases in which dietary factors are of great and, in some instances, paramount importance. These are hereditary or familial diseases, sometimes called 'molecular' diseases. Diabetes, where the importance of diet is widely recognized, has an hereditary component. In galactosemia, the removal of galactose and therefore of milk from the diet appears to constitute an effective treatment. Infants with phenylpyruvic oligophrenia appear to develop more nearly normally on a diet low in phenylalanine tryosine and tryptophane. Other diseases of this group, also, are related in an important way to dietary factors and considerations.

DISCUSSION

FREDRICK J. STARE

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MAY I JUST COMMENT briefly on some of the points mentioned in Dr. Daft's paper.

1) Enrichment of staple foods is important in principle and practice, but I do not think we can give it too much credit for the virtual disappearance of the classical deficiency diseases in this country in the past 25 years. Improvement in the standards of living, with more people being able to purchase meat, milk and eggs, has also been important in this regard; and I would like to think that some of the efforts in nutrition education by both the government and industry have been helpful.

2) I certainly agree with Dr. Daft that complacency is not justified with regard to the disappearance of deficiency diseases, but I doubt that our margin of safety is not large. In fact, I think our margin of safety for the classical deficiency diseases in this country *is* large.

3) World nutritional deficiency diseases do constitute an important challenge to all of us, but we through our government are not meeting this

challenge. Two months ago in Washington the President and Vice-President both participated in the National Food Conference. Both put in a plea for support of the Foreign Aid Program, largely on the importance of food and nutrition programs to the health and welfare of other people of the world. Yet I wonder if either realizes that technical assistance in nutrition in our Foreign Aid program has been nearly nil, and that beginning July first 1958 it will be nil! Three years ago I remember hearing Dr. Milton Eisenhower and Mr. Harold Stassen, who had both just returned from a trip to South America, speak of the great importance of technical assistance in nutrition in South America. Mr. Stassen laid plans for including nutrition activities in the technical assistance programs of South America, but then he took a new job. His successor did not follow through; in fact, in public health and nutrition he emphasized the negative. The present head of our foreign aid program has been in office for six or seven months and so far is only in the appreciation stage with regard to technical assistance in health matters.

4) I agree with Dr. Daft on the importance of obesity, atherosclerosis and fluoridation as public health problems involving various aspects of nutrition.

5) I should like to give added emphasis to the possible future role of nutrition in diseases in which hereditary and genetic factors are important. In addition to diabetes, galactosemia and pancreatic fibrosis, may I add that such common diseases as most cardiovascular diseases and dental caries involve strong genetic factors.

Now I should like to mention briefly a few other aspects of nutrition which in my opinion will be important in public health in the next 25 years:

An increasing awareness of overnutrition—more is not necessarily better in nutrition. One does not have to belabor the hazards of too many calories. Evidence is increasing of the potential hazards of too much vitamin D and too much calcium both in children and in adults. In the former I refer specifically to the syndrome hypercalcemia of infancy and in the latter to the influence generous intakes of vitamin D and calcium may have on the formation of kidney stones, soft tissue calcification and excessive calcification in joints. May I point out that ill health in man, any place in the world, is practically never associated with dietary calcium lack; that calcium balance, and even positive balance, is obtained on an intake of 0.25–0.3 gm; and I venture that few in this audience have a dietary intake in excess of 0.5 gm per day. Further, excessive intakes of calcium and vitamin D do not prevent or treat osteoporosis which is primarily an endocrine disturbance.

Interpretations of interesting laboratory findings, in terms of possible improvements in public health, are frequently difficult, particularly in the area of nutrition, and in the future may become more so. For example, in my opinion, the formula feeding studies of recent times do not justify an increased consumption of corn, cottonseed or safflower oil by the public. The findings that increased dietary magnesium retards the development of atheromata in growing rats do not justify recommending Epsom salts to the public.

In the next 25 years I hope we will have an increased emphasis on nutrition education, particularly in our elementary schools, in the hope of improving food habits for later years, and in the health professions—physicians, nurses and health educators. Under education I should like to include a plea that every member of this organization has a personal responsibility to combat misinformation—food faddism—whenever it raises its ignorant, stubborn and profitable head, even at the expense of a certain amount of personal invective that is most likely to come your way.

Chemical additives in food technology and insecticides and pesticides in agriculture have important roles to play in our food economy, but as in the past, so in the future we must maintain a constant vigil regarding their safety.

Nutrition in the future has important implications in mental disease.

The next 25 years will see important developments in radiation to which nutrition will relate. This involves not only the use of radiation in the preservation of food but what effects it may have on the utilization and metabolism of various nutrients.

Lastly, may I give added emphasis to global nutrition. I hope that sometime in the next 25 years we will have a Foreign Aid program that gives more than lip service to the importance of technical assistance in nutrition. A few months ago, when in New Delhi, I was surprised to learn that a couple of years ago the Russians provided most of the staff of the Children's Hospital in New Delhi. No doubt this is a small contribution in their total foreign aid program, but I venture to say an important one from the viewpoint of the 'common man.' Why don't we through future foreign aid programs provide cooperatively with other countries a half dozen INCAP's—two each in South America, Africa and Asia?

Where are we headed in Public Health Nutrition? We are headed for many important and exciting discoveries that cover the range from energy metabolism to the latest trace mineral, and with benefit to the health of all the peoples of the world.

ROLE OF THE HOME ECONOMIST AND DIETITIAN

E. NEIGE TODHUNTER

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IN ORDER TO EVALUATE EFFECTIVELY the role of the home economist and dietitian we must know what these terms stand for—'look behind the label' as it were. It is logical to look to the dictionary; but this is of little help because it does not mention 'home economist'. Popular concepts of the home economist are many, varied and mostly quite erroneous. The dietitian according to popular belief and also by the dictionary (which after all does not give meanings, but rather current usage of words) is one concerned with planning meals for the sick.

Justice Holmes once said, "a page of history is worth a volume of logic", therefore, let us turn back very briefly to history. In 1894, Congress appropriated $10,000 "To enable the Secretary of Agriculture to investigate and report upon the nutritive value of the various articles and commodities used for human food, with special suggestion of full, wholesome, and edible rations less wasteful and more economical than those in common use" (1). This work was assigned to the Office of Experiment Stations under Dr. W. O. Atwater who has been called 'the father of American nutrition'.

Just five years later, in 1899, a group of women met at Lake Placid, New York, in what was the first of an historic series of annual conferences (2). These eleven women chose the name 'home economics' to represent the work of their group. The following year a discussion of hospital dietaries was on the conference program, thus officially recognizing the work of the dietitian. Dr. Atwater was present at the third conference in 1901 (he had been invited to the first two, but was unable to attend) and reported to the home economists on nutrition investigations he was conducting.

In the summer of 1902, home economists from all over the country and also from England and Japan went to Wesleyan University, Connecticut, for a summer school in chemistry and biology (3). The program included lectures and laboratory work from Dr. Atwater on methods and results of food and nutrition investigation; from Dr. Langworthy on experiments on nutritive value and digestibility of foods; and from Dr. H. C. Sherman on methods of food analyses. Each year the Lake Placid Home Economics Conferences gave a prominent place to discussions on nutrition. These conferences culminated in a national meeting in January 1909, when the American Home Economics Association was founded; and in 1917 a group with more specialized interest in dietetics separated off to form the American Dietetic Association. This latter group had as its stated objective 'to improve the nutrition of human beings' and for its motto 'To benefit as many as possible.'

This brief excursion into history shows what is 'behind the label'. The term 'home economics' covers a very broad field; it is concerned with the home and family members and therefore with the subjects of food, clothing, shelter, and also child development, human relations, art, household equipment, management and finances. Since no one home economist can be expert in all these areas our discussion here will deal with that home economist who concerns herself with problems of food and nutrition. We will let her history be her definition, and for the dietitian accept the official definition, namely, "a member of the profession of dietetics which deals with the science, technical aspects and art of feeding people" (4). A dietitian usually is one who has graduated in home economics, so a dietitian is a home economist but not every home economist is a dietitian!

How well have the home economist and dietitian followed up their early interest in the newly developing science of nutrition? They entered this field, I believe, because of their inherent interest in people and in human welfare. Because of a desire to work with and for people, their work in food and nutrition has been dominated, directly or indirectly, by the questions: What are the nutritional needs of humans? How will these studies affect humans? How can this scientific information be used for the improvement of the health and well-being of people?

RESEARCH

The role of the home economist and dietitian has not been one of passive acceptance of re-

search information, but an active one of participation in human research studies.

The home economist began her research in the days when small animals provided the only means of vitamin assays. She worked for many years with guinea pigs. Rats and microorganisms too served as her tools, but whenever newer methods and equipment have developed to make possible quantitative studies on humans she has carried on her investigations in that field. A glance at the annual report of home economics research in the experiment stations (5) shows publication of studies dealing with the nutritive value of various foodstuffs; the effect of processing, storage and cooking methods on the nutritive value of foods; nutritional status studies of various age groups; metabolism of minerals and vitamins by young children, adolescents and older women; utilization of nutrients by elderly women; energy requirements at different ages and for different activities; dietary studies and surveys.

Much of this work has been limited. Limited, because often there has been only one home economist in a laboratory. She is not a biochemist, and she is not a clinician—no one person can be everything in research. But because she has a consuming interest in the health and welfare of women and children she has steadily worked away at what she could do within the limits of her training, facilities and equipment, and one pair of hands. She has frequently been the only one with patience and persistence to tackle the tedious details of human metabolic experiments. She has had the courage to explore in this field when she was aware that the tools and technics were not yet all adequate for the purpose, and that the results were not always easy to interpret.

Has there then been a significant contribution in nutrition research on the part of the home economist? One must seek the evidence in the research journals. It also seemed reasonable to look over the references used by the Food and Nutrition Board of the National Research Council in determining the 1953 Recommended Dietary Allowances (6). Some 255 different papers are cited as the basis of those recommendations and of these 69 or approximately 27% have a home economist as author or co-author.

The home economist has been aware of some of the limitations on what she can do alone in human nutrition. She is aware that her training and experiences are different from those of the biochemist, statistician and clinician, but that she has a special responsibility and a specific contribution to make. Therefore, she has teamed up with her counterpart in other states in the region and with research workers in other disciplines and has engaged in cooperative research work. As an example of this the North Central Regional Cooperative Project on Nutritional Status and Dietary Needs of Population Groups (7) may be cited. She has learned how to be a member of a team, to do careful group planning and checking of technics, to carry through on the experimental work and to help in the preparation of the final research report. With this background she is prepared now for the role of a member of the team which must work on the nutrition problems that lie ahead—and for the future, the problems are many. We need more research studies on human beings—long-term studies preferably over a number of years. Some work has been done on nutrient interrelationships, but methods need to be devised for studying these in a mixed diet; more studies are needed on the effect of nutrients on human performance—emotional and intellectual as well as physical; research is needed on the nutrition of the aged, and on nutrition in relation to longevity. These problems will need an interdisciplinary team approach and will need the home economist in the planning and execution of such research studies. Similarly the dietitian is needed on the medical team in such studies as nutrition in relation to obesity, and to chronic and degenerative diseases.

This is the satellite and guided missile era. And so we must think of related research problems. As we look at what has happened in the last several months and consider the current discussions of space travel, what once seemed fantasy is now rapidly nearing reality. We have not yet learned how to help the wives of jet pilots give their husbands the proper diet and we must consider the nutritional needs of space travelers; also the nutritional needs of scientists and engineers concerned with rockets. Are they any different from others, and does nutrition in any way influence split-second timing, coordinated reaction and alertness of mind?

INTERPRETATION AND APPLICATION

The importance of research does not need to be emphasized here, but the responsibility for wise interpretation and application of research findings does need emphasis. Research is frequently regarded as among the highest levels of endeavor and application and interpretation as being a job anyone can do. Either job may be done well or done badly; our concern is for each to be done well because each is mutually sup-

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portive. Progress without research is not possible and research without wise interpretation may be a source of personal satisfaction to the individual investigator, but has no real worth to the society in which we live.

Interpretation and application of nutrition has been a major responsibility of the home economist and dietitian. Their professional interest is directed to service to people; their training and experience qualify them to do the job which we might call the sociological side of nutrition. A greater number have been engaged in this second phase of nutrition work than in research. The dietitian is a teacher of medical and dental students, internists and nurses, also of the patient and the patient's family. This she does in the classroom and seminar, at the bedside and in the clinic. The home economist teaches at many levels; in college to the professional and the general student, and in high schools and elementary schools. Much of her teaching is more informal and is to various groups through which she reaches homemakers, men and women in industry and rural families. Many home economists accept invitations to give lectures and to appear on radio and TV.

Not only oral communication is used in the attempt to take nutrition information to the people. We find contributions in books, magazines, newspapers; in pamphlets from the American Dietetic Association, public health and welfare agencies and in cooperation with business and industry. Much effort has also been given to the school lunch program.

We, as home economists and dietitians, have long been working in this way but we have not yet reached our goals. Many groups are not yet being effectively reached, as for example the teenagers, the older age group and those who live alone.

As we look to the future we must do more experimenting with new or different methods of teaching and interpreting. We must look for new approaches, new tools and new ways of making the subject interesting and of vital concern to each individual. We need to be more critical and analytical about the procedures we use, and try to develop ways of measuring the results of our teaching. We need research on such simple but vital questions as why do people eat what they eat? What determines what people will eat? How can we motivate people to want to modify their familiar food patterns or improve their food habits?

The food faddists and the quacks seem to be with us always. Their motives do not change, but with each generation they skilfully manipulate the discoveries of the science of nutrition to serve their own ends—the promotion of some particular food or preparation of nutrients. Half truths, distortion of facts and subtle innuendoes are the stock in trade of this group. To combat this a most vigorous campaign of nutrition education is needed for the homemaker, so that she may spend her money wisely and get the greatest nutritional return for the money expended. Also, a program of nutrition education in schools is needed so that children may grow up knowing the facts about essential nutrients and the foods that will supply those nutrients. The American Dietetic Association is working to combat food fads and misinformation and has a recent publication (8) which should be helpful; and the Nutrition Education Conference held in Washington, D. C., in April 1957 (9) was an example of home economists working with other groups on this problem.

Effective nutrition education for all people, and that must be our goal, cannot be achieved by home economists and dietitians alone. It will take the concerted efforts of all in the biological sciences, the behavioral sciences, education, agriculture and the food industries. It probably needs what has been proposed elsewhere—a Nutrition Education Foundation.

Meal planning and food preparation are not ends in themselves, nor is eating solely a matter for sociability and personal enjoyment. These are the stepping stones to good nutrition which contributes so markedly to vigorous, productive and enjoyable living.

Unfortunately there has long been in the minds of the public the impression that if a meal is nutritious it cannot be enjoyable. The home economist has a responsibility to show that meals can be simple; that food which is served can be appetizing and satisfying and at the same time meet all nutritional needs. Some progress has been made, but much yet remains to be done. This is one area which is a direct challenge to the home economist and until she succeeds in meeting this challenge we cannot achieve nutritional well-being for all the population.

And in the practical interpretation of nutrition, since the dietitian is so often in charge of the actual feeding operation, hers, too, is the responsibility to help people achieve good nutrition. She must maintain high standards for institutional diets—food that is good to look at and good to eat; food that is planned and prepared in

accord with the cultural patterns of the group; food that is selected with a real understanding of human behavior and of what motivates food choices.

INTERNATIONAL ASPECTS

Food and health are not only of concern to the family and to the nation but are recognized as world problems, as witness the work of FAO, WHO and UNICEF. Contributions to these world nutritional problems may surely be regarded as one of the factors in world peace. Home economists and dietitians for some years have been serving abroad in programs of feeding children, evaluating the dietary practices, the nutritive value of available foods in use or that might be used, different methods of food preparation, and improving the nutrition of pregnant and nursing mothers and of the whole family. They have aided in the setting up of dietary departments and home economics programs in other countries and have stayed to teach and help in the training of the native and local teachers and leaders. This is a role that should be extended and expanded if nutrition is to reach its target of improved nutrition for all people everywhere. But again, the home economist and dietitian can be far more effective in using their own unique qualifications for combat of world undernutrition if they are given the opportunity to work on a team which also uses the unique attributes of the clinician, the biochemist, the anthropologist and the agriculturist.

If this seems to you a glowing or over-optimistic picture of the abilities and contributions of the home economist and dietitian, let me assure you that these are documented statements.

Thus far I have tried to show that the home economist and the dietitian have a part in the continuous research program that must go forward in nutrition. Not only in laboratory research in human nutrition, but in the more difficult areas of human behavior with regard to food, of evaluation of dietaries and dietary practices, and of nutrition education for all ages and all groups. These are some of the more difficult areas, because we are uncertain of the procedures to use, we lack the methodology and the tools for measurement—and sometimes even the certainty of what to measure. However, it might be well to recall that when the vitamin concept was in its infancy (and many denied that such unknown food substances could exist) research workers, including home economists, went ahead and developed methods for measuring these unknowns and were able to obtain fairly good tables of vitamin units and comparative vitamin values of foods. The same research spirit must lead off into the present areas of the unknowns.

OUR ROLE FOR THE FUTURE

One difficulty in fulfilling our role in the future is that in home economics and dietetics we face the same problem which is attracting national attention—the shortage of scientists. There is a serious shortage of professional home economists and dietitians, and the increasingly early age at which young women marry today seems to preclude or render unattractive the essential basic training in science and the years of graduate training required for effective work in foods and nutrition. We need a new approach to education for living in today's world. A world of science and satellites needs people trained in science, but there must be a balance between basic science, biological sciences and the social sciences, that is, the human factor in living. Groups such as assembled here can fully appreciate the significance of this and should take the lead in working for educational programs that demand discipline of the mind, and hard mental work that develops the thinking abilities of young people, and that provides balance in the subject matter areas. In such a program the home economist and dietitian will have to broaden and strengthen the base of training for young people and be more imaginative regarding their own profession and the contribution it can make.

There are many in our profession who are thinking hard about the problems in nutrition now and for the future. They are thinking about more and better training for the job, strengthening their science background, learning more about human motivation and behavior, learning how to be more critical of their own work and preparing themselves to cooperate more efficiently and effectively with others on the nutrition team. They are doing this because they belong to that band of practical but scientific visionaries who see in the not-too-distant future all people everywhere well fed. An end to be achieved only through research, interpretation and application of nutrition knowledge.

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DISCUSSION

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WORLD PROBLEMS in nutrition offer a challenge to home economists, whether we serve in an advisory capacity in other lands or here at home, guiding the work of foreign students. Adaptation of nutrient allowances, methods of food preparation and so forth, to different situations calls for experience and imagination. The potential value of increased food crops may be lost if innovations are made without careful study of their probable effects, including those on the home. This calls for team work among home economists, anthropologists and agricultural scientists. Can the hybrid corn be ground on the old mill, and will it make good tortillas? If an improved variety of mung beans yields a much larger crop, how will this affect the pattern of housekeeping, food preparation and child care by the women who have customarily harvested beans? As an observer in one Thai village, I saw the start of an attempt by the Thai government to introduce culture of tilapia, a rapidly growing fish. Five years ago, three households had obtained tilapia fingerlings from the demonstration pool maintained by the district officer. During the next two years more than a hundred families in the village tried tilapia culture, but a member of our research group who was there last summer reported that none had persisted. Some said that no one liked this fish. Suppose that the people had been taught to regard tilapia culture primarily as a way of increasing the home food supply and thus improving the family health, rather than as a means of supplementing income; suppose that Thai home economists had devised familiar and acceptable ways of using this unfamiliar fish, and that education along these lines had paralleled the introduction of tilapia culture. Might the story have had a different ending? I have heard that this approach is being used in an experiment now in progress in another part of Thailand where supplies of protein are low. In introducing fish flour, people have been shown how to use it in making fish paste, curries and other everyday foods. We will watch this experiment with interest. The patience and persistence to tackle tedious details, which Dr. Todhunter has mentioned as essential in carrying out human metabolism experiments, is equally necessary in this field if suggested improvements in food production are to bear fruit in better nutrition for families everywhere.

NUTRITION AND FOOD PROCESSING

H. E. ROBINSON

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THESE ARE REVOLUTIONARY TIMES in the food industry. In the past quarter of a century the food packers have become food processors. Gone are the days when the food industry supplied only basic items such as meat, milk, flour, oranges, potatoes and so forth. Instead there has been developed an intricate system for processing raw materials into consumer type products tailored to meet the customer's demands. All this is in line with the objectives of the food processor: to make available to every citizen a variety of attractive, palatable, convenient foods providing nutritional needs at a reasonable cost.

Today, through better nutrition education, the public is demanding more nutritious foods. The processor can supply them and has in many cases led the way in promoting these more nutritious food products. Education of the public to their nutritional needs and to the ways in which these needs can be met is an essential prerequisite to the successful marketing of any improved food product.

One thing which we can say with certainty about the future is that we are going to get *better* foods. They are going to be better because we have available today improved equipment of many types with which to conduct the processing operations. We have a better understanding of the chemical nature of the products, and of the biochemical reactions which take place under various conditions. In addition we have a more thorough concept of the nutritional significance of the various components of these foods and an appreciation of the many psychological factors involved in the selection and utilization of foods. Food processing is indeed undergoing a revolution, changing from an art to a science.

APPLICATION OF NEW MECHANICAL PROCESSES

The development of continuous and more rapid food processing procedures has improved nutrient retention and food quality and has also provided economies in operation and production.

Illustrative of this trend are the recent efforts made to decrease the period of the heat treatment by using higher temperatures and by improving heat transfer to the food either by mechanically increasing movement of food within the can or by pre-heating or pre-sterilizing the product before filling the can. Several types of systems have been developed and are being put into commercial practice. *1) Agitation retorts*, a process wherein the product within the can is constantly in motion making heat transfer more rapid. *2) Asceptic canning*, a method in which the product is sterilized and cooled outside the can then filled and closed in sterilized containers. *3) Pressure chamber canning*, has been tested, but it has so far not been commercially successful. In this method a product, canning equipment and employes to operate it are enclosed in a pressure chamber. The product is sterilized and then filled into cans and sealed while at elevated temperature.

Since extended periods of exposure to heat cause deterioration of quality, any means of decreasing the severity of the process may be expected to reduce the loss of nutrients. The effectiveness of the newer procedures is shown by marked decreases in the processing time for foods canned in an agitating retort. When agitation is used, higher temperatures may be employed. The movement of the contents of the can minimizes burning at the surface which occurs at temperatures about 240°F when there is no agitation. Such marked decreases in the heating time, made possible by rotating the cans to create convection currents within the contents and thereby transferring heat from the surface to the interior of the can more rapidly, improved flavor and promoted retention of nutrients. Thiamine, for example, being quite heat-labile, reflects this increased nutrient retention.

These more rapid canning processes are most applicable to fluid or semi-solid products, but certain types of meats such as meats for infant feeding may be processed in these ways.

Conventionally the raw chopped meats for

frankfurters are stuffed into casings (natural or artificial) hung on smoke 'trees', allowed to stand at room temperature for up to several hours for the cure to develop and then smoked and heat processed for about four hours to an internal temperature of 160°F. They are then spray washed first with hot then with cold water. After surface drying they are removed into refrigerator coolers for several hours, to be chilled to an internal temperature of about 40°F.

A newly developed process for frankfurters is one in which the chopped meats are automatically introduced into molds where the application of high frequency electric current for a few seconds sufficiently coagulates the meat mass so that it retains its form when ejected from the mold onto a continuous conveying system. The conveying system carries the product through heating and smoking chambers and finally through a chill tunnel. Total process time from the extrusion into the mold to the chilled packaged product being on the order of 95 minutes, 60 minutes for heating and 35 for chilling. Further modifications of the process are expected to reduce the total process time to 45 minutes. While no specific data are available on improvements in quality as a result of this process, the reduced time of exposure to heat may be expected to increase retention of nutrients and improve quality.

Dehydration is one of the oldest methods of food preservation, yet not until recent years have advances been made which have greatly improved the quality of many of these partially or completely dehydrated products. Now, many very acceptable dried dehydrated foods are appearing, e.g. soups, potatoes, coffee. The availability of equipment to dry products at low temperatures, even from the frozen state, must be given much of the credit for these developments. The vitamin C content of oranges varies considerably and at times fresh oranges purchased in the open market in Chicago have ascorbic acid values as low as 14.5 mg per 100 ml of juice. By picking the oranges at the proper time and by application of new methods for water removal the juice manufacturers have been able to attain uniform ascorbic acid levels as high as 60 mg/100 ml of juice.

Dried skim milk has been used for livestock feeding and for some food preparation for many years, but it has never had good customer acceptance as a retail item. Recent improvements, such as the development of a wetable and readily dispersible skimmed milk powder, have increased the use of dried skimmed milk in the household. So far no one has produced a completely acceptable dried whole milk commercially, but the problems standing in the way of this development will undoubtedly be solved in the not-too-distant future. Shelf stable, condensed whole milk comparable to bottle milk in flavor has been developed.

Many other processes of a rapid and continuous nature which will reduce the severity of heat treatments are being developed and applied. The net result will be an overall improvement in commercially processed foods.

APPLICATION OF NEW CHEMICAL KNOWLEDGE

The mechanical improvements would not have been possible without a thorough understanding of the nature of the foods involved. No group knows better than this one the tremendous strides which have been made in understanding the chemistry of biological materials during the past few years.

The use of anti-oxidants in edible fat today has made it possible to use fat in a considerable number of products without causing deterioration of flavor or nutritive value formerly caused by autoxidation of the fat, and has made possible the blending of eggs, flour and shortening into shelf-stable cake mixes. The use of enzymes for removing glucose from whole eggs, whites and yolks, has likewise improved these products. Not only are they suitable for incorporation into consumer-type items, but in addition have undoubtedly been improved nutritionally.

The use of meat tenderizers today on cuts of meat which formerly would be regarded as not having enough fat marbling or fat coverings to be tender will make leaner cuts of meat more acceptable. These tenderizers may change the entire concept of marketing beef animals.

The vitamin fortification of foods was started because of our knowledge of nutrient loss during processing. Fortification has unquestionably improved the nutritive quality of these products. Fortification of food with other chemicals is being talked about and acceptance of these practices will undoubtedly be based on nutritional soundness.

The application of antibiotics to foods for their preservation employs another biological prin-

ciple which is being intensively studied and which may under proper conditions have an effective role in food processes. At present, however, except for limited application in poultry meat there is insufficient evidence of its safety to permit use in foods.

Knowledge of the chemistry of meat pigments has aided in the development of suitable packaging materials for meats. Without these new films and coatings pre-packaged meats would not be popular, since the cut surfaces discolor quickly unless properly protected.

APPLICATION OF NUTRITIONAL KNOWLEDGE

Nutritional needs have likewise influenced the types of foods marketed and will probably have more influence in the future as the public gets a broader understanding of the importance of nutrition and how to properly use their various foodstuffs. There is little doubt that our nutritional needs, particularly with reference to calories, have changed. The decline in a need for calories has not been paralleled by a decline of needs for the many essential nutrients. In fact, surveys conducted throughout the country have indicated that many of those individuals who have high intakes of calories still have deficiencies of one nutrient or another. If we can rely upon these surveys then there are sizable segments of our population which could improve their nutritional status by better eating habits. Foods designed to fit these new nutritional needs, which are primarily for products which have a lower calorie contribution, but which provide the usual quantities of other nutrients, are appearing on the markets.

Some of these foods are simply modifications of previous products. Perhaps the simplest illustration is the closer trimming of meat products to reduce the quantity of fat sold. Diabetic fruits, vegetables and ice creams, low sodium foods, low fat foods and many low calorie items now appearing are reflections of the demand for nutritionally controlled foods. While many of these are faddist items, there is obviously a market for this type of product and we can expect to see other evidences of this demand for foods which have special nutritional characteristics desired by certain groups of people.

In this same connection there has been a great deal of interest in the types of fat available for shortening and seasoning purposes. At the present there seems to be no sound reason for a change in the types of fat provided. However, should subsequent research indicate that one type of fat is preferable to another the processing industry can be expected to provide the preferred type.

Currently, most housewives prefer solid or 'plastic' shortenings rather than oils, although the liquid fats do have some advantages with respect to convenience. This preference is based upon the superior performance of the plastic shortenings when used for a variety of purposes, such as frying, cake making, pastries etc. Liquid shortenings which perform satisfactorily for one of these uses have less satisfactory characteristics when used for a different purpose. If any major change is made in the shortening industry it would require new concepts of the use of fats, revisions of cooking techniques, recipes etc.

There is one nutritional area in which there is a need for special dietary consideration which has not yet been serviced by dietetic foods. This is the area of pregnancy and lactation. Although the pregnant woman or nursing mother does not have to eat for two, as was once thought, nonetheless her nutrient requirement is increased. Her need for calories and proteins is increased as well as her requirements for calcium, iron and vitamins A, B_1, riboflavin, niacin and C. Also she needs vitamin D which the normal adult female does not require. A few women have difficulty maintaining an adequate caloric intake, but a majority have a problem with too many calories. The situation is reversed with other nutrients. According to Dr. W. T. Tompkins, in his chapter on 'Nutrition In Pregnancy' in the book, *Modern Nutrition in Health and Disease*, few individuals if any are able to meet the increased needs of pregnancy without suffering some degree of deprivation. There is a degree of deficiency in relation to the stress applied that is critical, not merely the existence of a deficiency, for all patients are probably deficient in some respects. He further states, "Several clinics have shown that the higher the quality of essential nutrient intake with a caloric intake sufficient to meet individual energy requirements, the more successful the outcome of pregnancy."

Not only does an adequate diet have a beneficial effect on the mother, but the benefits are extended to the fetus. According to Tompkins, "Data available indicate that the status of the

infant at birth is a reflection of a nutritional status of the mother." Dr. W. J. Dieckmann of the University of Chicago has shown this to be true for protein nutrition and Dr. T. R. C. Sisson and Dr. Curtis Lund, of the University of Rochester, have shown a correlation between the iron metabolism of the mother and that of the child.

The close relationship between the nutrition of the mother and her baby present nutritionists with a golden opportunity to solve two problems at one time. This is why the nutrition of pregnancy and lactation is doubly important and more consideration should be given to dietetic foods designed specifically to fit this need.

APPLICATION OF PSYCHOLOGICAL KNOWLEDGE

So far we have dealt primarily with those factors which contribute to the production of foods. Perhaps consideration of the factors which induce consumption of foods or at least purchase of foods should be dealt with, since these factors are of extreme importance to the food-processing industry. Many times it is the shape of the package or the size of the print that determines which product the customer will buy rather than the quality of the contents. Reasons for the acceptance of certain foods and the rejection of others or for the popularity of certain advertising slogans are important to the economic success of any food processor. The successful utilization of information which can be obtained only by consumer research program is essential to continued success. The information obtained from these studies of consumer preferences may contribute little to the actual nutritive value of the food product, but they contribute much to the way in which it is presented and both the food processor and the nutrition educator must be aware of the reaction of the public to foods and the ways in which it must be presented for popular acceptance.

SUMMARY

Processing of tomorrow's foods will be geared to better nutrition. With the changing food habits of the American population the processor must strive to retain natural nutritive values or when necessary may actually improve their nutritive value through proper fortification. Knowledge gained today through research will be applied in tomorrow's food processing.

DISCUSSION

WENDELL H. GRIFFITH

From the University of California, Los Angeles, California

ONE MUST AGREE with enthusiasm that today's industrial preparation of foodstuffs for the market and the home is quite remarkable, indeed. The fantastic variety of neatly packaged and nutritionally acceptable items in our food stores represents a series of highly important achievements with respect to storage quality and durability, ease of transportation and convenience of distribution. Furthermore, there is no reason to doubt that improvements along these lines will continue to be made and that, in the future, today's supermarkets will be as outmoded as yesterday's country store

It is pertinent to note, however, that nutritional science, as represented by the membership of the American Institute of Nutrition, must continue to accept its share of responsibility for nutritional health. This will be true despite the significant advances that have been made in sanitary practices in food handling and despite the sincere endeavor of food processors to manufacture safe and nutritious products.

Nutritional science must ever be alert to the factors that determine the true acceptability of foods and not merely aware of the convenience of their packaging and use; alert to the contribution that each makes to the daily supply of nutrients and not merely appreciative of their newness or their modern character; alert to the success achieved in the retention of nutrients during processing and not merely concerned over the degree of restoration of nutrients that may be required; alert to the problem of the safety of foods and not merely gratified by the appearance of high quality; alert to the need of new sources of food during periods of accelerated population increase or in times of stress such as might result from wartime exposure of crops to excessive

ionizing radiation and not merely satisfied with the presumed adequacy of present resources and knowledge; alert to the necessity of intensified research in all aspects of human nutrition and not merely self-laudatory over achievements and apologetic over failures.

It is no denial of the success of the food industries to call attention also to the increased responsibility of the individual for his own nutritional health. Man, after all, is a biological organism who must retain his capacity to make decisions if he is to remain distinct from other animals. If these decisions involve the selection of his dietary, then he must be fortified with knowledge of food and food values and motivated with proper self-interest. Ignorance and indifference make no contribution to individual health and happiness, neither does the enticement of the too easy, 'the too tranquilized', way of life. One may hope that man will retain a modicum of his independent, even stubborn, ideas about his 'daily bread.'

In the words of Dr. Robinson, "both the food processor and the nutrition educator must be aware of the reaction of the public to foods and the ways in which it must be presented for popular acceptance." He has stated also that the processing of tomorrow's foods will be geared to better nutrition. This is a challenge indeed to both the processor and the educator to ensure that the public's know-how about nutrition makes corresponding progress.

DISCUSSION

WILLIAM J. DARBY

From Vanderbilt University School of Medicine, Nashville, Tennessee

DR. ROBINSON'S REPORT has admirably illustrated the thesis that the aim of the responsible food processor is to "make available to every citizen a variety of attractive, palatable, convenient foods providing nutritional needs at a reasonable cost." His conclusion that "knowledge gained today through research will be applied in tomorrow's processing" sets squarely on the shoulders of nutritional science and scientists a major responsibility for provision of the guide lines toward this aim. What, then, does this mean for us?

First, an increasing responsibility for the interpretation of existing knowledge in terms of food improvement—a major task in relation to consideration of such matters as food additives. The appropriate use of additives, according to the First Joint FAO/WHO Expert Committee on Food Additives, may serve to maintain or enhance the nutritional quality of foods, to enhance the keeping quality or stability with reduction in food wastage, to make foods more attractive, or to provide essential processing aids. On the other hand, inappropriate use may deceive the consumer, disguise faulty processing or handling, or be otherwise undesirable or injurious.

Similar considerations pertain for new methods of processing—such as irradiation, storage or packaging. These matters are of concern not only in regions of highly complex food industries but also in the technically less sophisticated areas. This vast and rapidly expanding field is faced with a serious shortage of personnel appropriately trained and oriented toward these aspects of nutrition.

As research scientists we must give more attention to developing methods of study and appraisal of the health benefits and safety of foods and food additives—and not only the new additives, but the time-honored ones as well. We must devise basic scientific principles for and approaches to the evaluation and interpretation of laboratory findings in relation to human health.

As educators we must evolve educational programs for training personnel to carry forward the research and scientific development in this expanding field. The scientists we train will be in new areas—food toxicology, nutritional psychology, nutritional anthropology, etc. These fields are assuming as definite form as did that of vitamin chemistry or of protein nutrition some years back.

The major immediate need, as I see it, is for properly oriented, basically designed education planned to develop young nutritional scientists to assume the leadership for these fields in the years ahead.

NUTRITION OF FOOD-SOURCE ANIMALS

DAMON V. CATRON

From Iowa State College, Ames, Iowa

NO COUNTRY IN THE WORLD today is blessed with the tremendous food producing capacity of the U.S.A.! Although the acreage for cropland in the United States has remained almost constant for the past 35 years, our highly nutritious and palatable products from animal agriculture—meat, milk and eggs—have paralleled our ever-increasing human population.

Although the trend is for fewer farmers working shorter hours on larger farms, they are constantly increasing meat, milk and egg production. Records show that their progress in efficiency has increased output as much in the past 17 years as during the 120 years from 1820 to 1940.

Quoting from *Food Power, U.S.A.* (*1*): "As a nation, the United States has 7% of the world's population—and only 13% of our people are farmers. Yet United States farm producers, representing less than 1% of the world's population, are responsible for 51% of the egg production, 41% of the red meat, and 46% of the fluid milk in the world!" Despite the rising index for costs of living, most protein foods—especially eggs and many meats—can be purchased for less money now than it took 10 years ago. The same methods of volume and efficiency in production that have made this possible should continue to make animal protein foods a 'good buy' in the future.

CONTRIBUTION OF FOOD-SOURCE ANIMALS TO MAN

As a Preferred Diet

Unquestionably, a greater yield of food nutrients per acre of land can be obtained by direct human consumption of certain selected crops than by conversion to animal products (2). However, most of the American public prefers a diet rich in animal products—meat, milk and eggs. As long as incomes are high and the size of the population permits, Americans are going to eat large quantities of meat, milk and eggs.

In Helping to Set a 'More Perfect' Table Nutritionally

The food products of our animal agriculture—meat, milk and eggs—have been shown by scientific nutritional research to be rich sources of essential amino acids, vitamins, minerals and unidentified nutritional factors. They have been classified, and rightly so, 'protective foods'. It is needless to extol in detail or to support with references from the voluminous scientific literature the outstanding nutritional values of the products from our animal agriculture as compared to cereal grain and other plant products commonly used in the human diet. However, the relative value of crop sources is increasing as their deficiencies are recognized and can be supplemented by synthetic forms of these nutrients.

Trends in our eating habits show that the per capita consumption of fruits, vegetables and poultry and dairy products is going up at a rather rapid rate. The use of meats and fish and poultry is also increasing. However, there is a definite downward trend in the consumption of cereal products and potatoes. These trends have been induced by the increasing 'calorie-consciousness' of the American public.

As 'Concentrators' and 'Up-Graders' of Nutrition

As pointed out by DeGraff (3), the annual crop harvest of the United States, including cereals, legume and oil seeds, potatoes, fruits and vegetables etc., is sufficient to feed 500 million people at upwards of 3000 calories per person per day, if we were to use our crop products in the oriental manner—to provide an oriental-type diet. Furthermore, the 40-ounce capacity of the human stomach sets up a physical limit on how many pounds of food any one of us can eat in a day or year.

Livestock and poultry then serve as 'concentrators' and 'up-graders' of unpalatable and less nutritious crops into highly palatable steaks, chops, milk and eggs.

We can neither consume our total crop output as such or sell in world markets the surplus crops above what domestic consumption would be if the present 173 million Americans were to eat in the oriental fashion.

We normally feed livestock approximately 75% of our total tonnage of all harvested crops—

in addition to all the forage produced on pasture and range lands. Roughly, one-half the food in our average per capita diet is plant products from 15% of the cropland equivalent—while the other half is livestock products from 81% of the land resources. Therefore, livestock production creates a 'balance wheel' in the relative proportion of plant versus animal food-sources for human consumption.

Economics of Conversion—Feed to Food

This evolves around the utilization and conversion of energy and nitrogen (pre-formed protein or non-protein nitrogen) from the unpalatable and/or inedible to the palatable and edible form through animals. Based on 1956 harvests, 72.6% of the total harvested tonnage of crops was used as livestock feed.

Modern feed to food conversion ratios in our various food-producing animals vary considerably, and the whole story is not told in merely citing feed efficiency figures based on either experiment-station or farm-production records—which should be used with caution. Based on present average experiment station records, it requires 8 to 9 lb. of a combination ⅔ grain and ⅓ hay to put on a pound of beef on finishing steers. Lambs would require 9–10 lb. of 50–50 grain and hay to put on a pound of gain. However, it must be pointed out that these two classes of ruminant animals consume relatively large proportions of inedible range grasses, poor-grade roughages, corn cobs and silages—especially during the reproduction and lactation periods.

In the production of milk, dairy cows require about 1 lb. of grain and 2 lb. of hay to produce 5 lb. of a 4% butterfat milk. In this case, higher grade roughages are required than for beef production.

More direct comparisons can be made in non-ruminant animals. Growing-finishing swine require from 3 to 3½ lb. of grain and supplement to put on a pound of pork. Broilers, our most efficient convertors, are down to about 2.5 to 2.75 lb. of complete ration per pound of gain. They represent the epitome of perfection in converting feed to meat. It takes about 4 lb. of complete ration to produce a pound of turkey meat, and about 4½ lb. of complete ration to produce a dozen eggs. Based on present rate of development and application of technology, the rate of improvement of conversion of feed to food by food-source animals fails to keep up with our population increase. This could force a shift in human consumption from animal to plant products and eventually from conventional plant products to the use of algae, fungi and bacterial source foods.

GENERAL TRENDS IN ANIMAL NUTRITION

This involves a combination of what we will feed, where it will come from, how we feed it and the quality of the animal product produced.

Trends Toward Maximizing Efficiency of Production

1) More scientific 'know-how' is being applied from the basic sciences of biochemistry, bacteriology, physiology, endocrinology and enzymology in nutrition research to attain maximum genetic potential in production of edible animal products.

2) The nutrient requirements of the different stages of the life cycle of animals are being integrated into more efficient life-cycle feeding programs.

3) Developments in crop harvesting, processing and storage technology are encouraging the more efficient utilization of the entire plant (grain, forage, stock and cob) to be harvested as animal feed. The grain will be used largely by the non-ruminants and the roughage green-cut or preserved as silage for ruminants. This approach maximizes the utilization of crop production by the various species of food-producing animals.

4) Fewer, but larger production units (farms) are developing with more specialization, greater automation and confinement feeding on a production-line basis.

5) During the last decade, we have seen the beginning of an important development in animal nutrition, and that is the use of industrial products (both primary and by-products) in animal feeding. The chemical and pharmaceutical industries have awakened to the great potential market for amino acids, vitamins, hormones, enzymes and miscellaneous feed additives in the production of meat, milk and eggs.

6) It appears that the animal's ration will not only serve as a source of nutrition, but also as a convenient vehicle for chemotherapeutics for the prevention of disease, anthelmintics and systemics for the control of internal and external parasites, hormones for 'short-cutting' genetic improvements, and enzymes for increasing efficiency.

7) Engineering and feed technology are changing the methods of harvesting, processing, storing and the actual mechanics of handling animal feeds. Pelleted complete rations, which improve feed efficiency and enable us to get more total feed into the animal for faster gains, are growing in popularity. The development of field harvesting equipment and the problem of bloat on pasture is increasing the use of green-cut forage drylot-fed—especially for dairy cattle. The development of air-sealed storage and the desire on the farmer's part to work with the weather instead of in spite of it is increasing the use of high moisture grain (28% moisture corn).

Improvement in Quality of Animal Products

1) *Meat.* Recent trends emphasize more lean and less fat in all kinds of meat; In pork, the emphasis is on the 'meat type' hog which will yield carcasses with more muscling and less fat. Recent research at the Iowa Station (4) indicates that certain chemical feed additives (i.e. 3-nitro 4-hydroxyphenylarsonic acid) may improve carcass leanness when fed to swine. In beef, the demand is for more commercial and good grades of beef with less demand for prime—again more lean and less fat! In broilers (chicken) the emphasis is on a plumper bird with increased tenderness and more meat in proportion to bone than the barnyard chicken of yesteryear. In lambs a more youthful carcass is desired with less aged mutton and the accompanying odor. The housewife is certainly making her demands for more lean, higher quality meats with built-in 'maid service' felt at the meat counter of the supermarkets!

2) *Milk.* There is less emphasis on butter fat and more on the non-fat nutritional values of milk. Milking parlors, closed milk flow systems, bulk milk cooling and handling all will further improve quality and total consumption of milk and milk by-products.

3) *Eggs.* Controlled nutrition in confinement, egg cooling and grading have and will further increase the quality and uniformity of this product.

There is more and more emphasis being placed on quality of meat, milk and eggs despite the fact that there are no large reserves of these animal products to feed us. There is less than a 10-day supply of red meat, chicken, eggs and milk in storage. Although there is approximately a 39-day supply of turkey, this represents only about ½ lb. per person. There are essentially no stored supplies of fresh milk. The production of milk must be geared to meet consumer demand. Seasonal overflows of fresh milk are siphoned off as butter, cheese and other dairy products.

TRENDS IN RUMINANT NUTRITION

Beef Cattle and Sheep

1) Increase in use of low-grade roughages and green-cut forages. 2) Pasture usage will decrease for steers but increase for breeding herds. 3) Use of silages will increase with new mechanical harvesting and handling equipment. 4) The use of urea will undoubtedly increase in proportion to pre-formed proteins, leaving the oil meals for the non-ruminants. 5) Use of the artificial rumen technique will probably increase the feed additives going into ruminant rations. 6) The use of hormones has looked best to date in beef and sheep nutrition. 7) The percentage of energy coming from grain in total rations will probably decrease.

For Dairy Cattle

1) Increase in use of green-cut forage. With greater mechanization, and the problem of bloat facing us on pasture, we may see the use of green-cut forage increase tremendously. With the increased use of green-cut forages, undoubtedly total pasture usage will come down. The increase in use of green-cut forages will tend to decrease the bloat problem and increase total yield of food nutrients per acre for milk production. This will encourage the use of more drylot feeding. A solution to bloat in dairy and beef cattle would deter this practice.

2) With better land utilization, the use of improved pastures and forages should increase. Dairy cattle feeding is built on a higher quality roughage program than is beef cattle feeding.

3) Dairy research workers feel that the use of both roughages and silages, corn and grass, will increase. New harvesting equipment for removing the entire plant from the field will increase the use of a combination of silage in the winter months and green-cut forage (soilage) in the summer months.

4) Better balanced rations are on the increase with a subsequent reduction of feed per pound of milk produced. Grain, as a percentage of carbohydrate in the ration, will probably increase to get a greater nutrient intake. It appears that the

entire grain-producing plant will find even greater usage in dairy cattle feeding in the future.

TRENDS IN NON-RUMINANT NUTRITION

In General

Rations for the non-ruminants in the future appear to be based on corn or milo and soybean oil meal with the chemical and pharmaceutical industries striving to develop nutrient and feed additives which will make these grain-soybean oil meal base rations nutritionally complete.

For Swine

1) With increased nutritional 'know-how', there is a greater trend toward the confinement rearing of swine. Swine producers are following the pattern of broiler producers by increasing volume, specialization and automation. *2)* We expect to see less use of pasture for all stages of swine production from farrowing to market, but about the same for sows during pregestation and gestation. Present research indicates that we will see a greater increase in the use of corn silage for sows as the swine business becomes more specialized with a greater volume on each farm. *3)* There will be an increase in the use of better balanced rations, which includes balanced proteins with amino acids, vitamins, minerals, antibiotics, arsenicals and unidentified growth factors. Accompanying this will be a decrease in the feed required per pound of gain. *4)* There is greater emphasis on controlled feeding by using complete rations or automatically-proportioned grain and supplement rather than by using the relatively inefficient method of self-feeding grain and supplement free-choice. *5)* With the emphasis on the use of more feed additives in complete rations or in proportionately-fed supplement and grain, there will undoubtedly be an increase in the use of formula (manufactured) feeds.

For Poultry

The broiler is the most highly specialized and most efficient of all of our farm animals that convert feed to food. *1)* The trend toward confinement production, which has already started, will undoubtedly continue in broiler, turkey and in caged layer egg production. Confinement rearing decreases energy wastage and gives the producer an opportunity to control his rations and the quality of product produced. *2)* Consequently, there will be less use of pasture range for developing pullets and to even a greater extent for broilers, layers and turkeys. *3)* As nutritional research pushes the frontiers of knowledge out even further, the feed per pound of meat or dozen of eggs produced will continue to decrease. *4)* There continues to be an emphasis on the use of high-energy rations in all kinds of poultry rations in order to decrease the feed per pound of product produced and increase over-all efficiency.

FACTORS INFLUENCING FUTURE NUTRITION OF FOOD-SOURCE ANIMALS

The following appear to be the major factors which will affect, in varying degrees, the trend in nutrition of food-source animals:

1) Rate of population increase in the United States and in the world.
2) The over-all standard of living and purchasing power of the people.
3) Status of the world—peace or war.
4) Relative technological advances (5)
  a) In grain and forage crop production—affected by developments in plant breeding, fertilizer, irrigation, harvesting, storage.
  b) In animal production—affected by advances in breeding, disease-parasite control, specialization, automation, controlled environment.
  c) In animal nutrition—affected by developments in vitamins, antibiotics, hormones, enzymes, fermentation products.
5) Rapidity in application of new research discoveries.
6) Government agricultural policy—both domestic and foreign.
7) Medical research on diseases associated with diet.
8) Impact of promotion and advertising on consumption of different foods.
9) Improvement in quality of meat, milk and eggs.
10) Utilization of feed-crop surpluses.
11) What makes the farmer the most money.

Continued research in the field of animal nutrition will undoubtedly improve the production efficiency and quality of the products from our animal agriculture. Livestock and poultry will continue to play a very important role in the future as 'convertors', 'condensors', and 'upgraders' of raw feedstuffs into highly palatable and nutritious steaks, chops and eggs—keeping Americans the best-fed people in the world!

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DISCUSSION

R. W. Engel

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Nineteen years ago, when the U. S. Department of Agriculture published the yearbook entitled *Food and Life*, noted men in the field of animal nutrition were invited to predict the future of nutrition research. One of the suggestions submitted by the late Professor E. B. Hart, University of Wisconsin, whose contributions to animal nutrition research extended over a period of a half century, read as follows: "We should catalogue all the factors involved in the nutrition of animals, learn how to assay for these factors in our foodstuffs, and then, in addition, determine the needs of these factors quantitatively for livestock. That is a big program, but it is the ultimate goal of any program for the development of fundamental knowledge of nutrition."

It is evident that the task with which we were charged by Professor Hart has not been brought to a successful conclusion. A glance at the tables of recommended allowances, prepared by the National Research Council committees on animal nutrition, reveals that we now have firm information on only a limited number of identified nutrients. I am sure Professor Hart would agree with us that the task of establishing well-defined nutritional requirements for the various animal species has been complicated by the numerous recent research results which bear on the problem of nutritional interrelationships.

Assuming sensible support for basic research in agriculture, and vigorous administrative leadership in research programs, several disciplines which are now developing very rapidly can be anticipated to come to bear on meat production, among them cytogenetics, biophysics, endocrinology, microbiology, biochemistry, and perhaps even neurology or psychology. Economic forces may lead to swine and cattle production in what amounts to 'broiler houses' and to other changes in feeding and management which are essentially industrialization, but the big breakthroughs are to be expected from intensive introduction of the basic sciences into agricultural systems. This is neither speculation nor prophecy; but a restatement of reliably established historical fact.

AMERICAN INSTITUTE OF NUTRITION

Symposium on Nutrition and Food Technology[1]

Chairman: JAMES M. HUNDLEY

AGRICULTURAL TRENDS AND PROGRAMS

O. W. WELLS

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I WISH THE SUBJECT which I have been given for this paper were simpler. We could lose ourselves by cataloging, discussing, and endeavoring to analyze all of the various agricultural programs which we have developed in the United States since the first appropriation of $1000 for distributing seed and collecting statistics was made by the Congress in 1839. Some of this is worthwhile, but even the more widely discussed or controversial farm programs actually have had only a secondary effect on American food habits and food consumption.

Or we could lose ourselves in statistics. There are more than enough agricultural statistics to allow as much discussion as one might choose, dry and learned as it might be, of agricultural trends over the last 5 to 50 years, perhaps with some forward-looking projections preferably centering attention on some date a considerable number of years ahead, say 1975. Such forward looks will, as a rule, allow those of us who know the United States is still a relatively young, rapidly-growing nation to come forward with optimistic forecasts for the future, while at the same time allowing reasonable explanations as to why such longer-run statements do not necessarily explain what may be happening within the next few years, say between now and 1960.

Actually, some attention to both these approaches is necessary in considering where we now are and the approximate forces which are likely to affect food consumption over the next few years. But the two basic points which I should most like you to hold in mind are:

1) Agriculture is always faced with a two-way problem: on the one hand, we should like to see—we believe that—American farmers deserve reasonable returns for their efforts and the use of their resources; on the other, of course, we want to see that American consumers have available not only those foods which assure good nutrition but which are also foods they like.

2) Our chief underlying interest is always in the current American market. Any successful farm program must assist farmers "to produce more of those things which consumers want most, less of those things they want least". Perhaps this sounds trite. But the grand strategy of the main farm programs is exactly this: to assist in reducing acreage and production of surplus crops, while encouraging shifts toward those products which can be successfully marketed.

America is a fabulous food market!

Some time ago the editors of *Fortune* observed that "of all the violent upheavals that have shaken and transformed the American market, none have been bigger or more baffling than those affecting food. Back in 1941, Americans spent $20 billion for food." Currently, "to the stupefaction of just above everyone who thought he understood the food market," Americans are spending about $1.15/day/person, over $400/year or for all 170 million of us some $70 billion total per year for food. "Over the past dozen years, the increase in U.S. food expenditures has soaked up more dollars than the increases in spending for homes, consumer durables, or automobiles—or even for all these combined."

Economists generally consider it axiomatic that the percentage of income spent for food declines as income rises, so imagine their surprise as over the last 20 years the flow of disposable personal income has increased enough to raise the average per capita purchasing power within the United States by two-thirds, while over the same years the percentage of disposable income

[1] Held in Chicago, Ill., April 17, 1957.

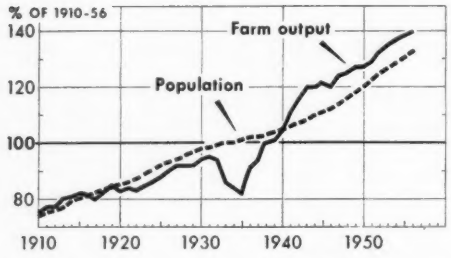

FIG. 1. Farm output and population—3-year moving averages. (U. S. Dept. of Agriculture.)

spent for food has increased by one-eighth.

With such a tremendous market at hand, why are we still so much concerned with farm surpluses? Perhaps the best answer I can give you is to call attention to figure 1 which compares the trend in farm output with the increase in the American population over the years from 1910.

Population was increasing over this entire time, farm output over most of it. That is, we are dealing with relative growth rates in our expanding economy. Farm output tended to fall behind during the years from 1920 into the mid-1930's—years in which the export demand also trended down and the rate of population growth here at home slowed down. Farm output then increased rapidly from the mid-1930's into the mid-1940's, stabilized for a few years, and then resumed a steady upward trend which has held farm supplies at a high level relative to population over the whole of the last decade.

We must always measure farm production relative to market outlets, including allowance for the fact that we still export some 7 or 8% of total farm output. With current rates of population growth, the American market would catch up with our farm output if it were only stabilized for a period of 3, 4 or 5 years. And this of course is the main effort which lies behind acreage allotments and marketing quotas for such cash crops as corn, cotton and wheat, as well as the new reinforcing program which we call 'The Soil Bank.'

As I indicated earlier, however, these acreage-allotment and related programs, including the Soil Bank, are not directed toward nor do they as a rule substantially affect food supplies actually available for ordinary consumer use within the United States. Of the main crops affected by these programs, cotton and tobacco are nonfood crops while wheat is a crop for which we produce each year a very sizeable export surplus and of which we have current stocks of about one billion bushels, or the equivalent of a full year's domestic consumption and export.

It is true that acreage allotments on corn do affect the feed base for livestock, but actual operating experience over the last several years has indicated that considerable acreages taken out of wheat and cotton have found their way into supplemental feed crops such as oats, barley and grain sorghums. So efforts to obtain some reduction in corn are necessary to simply balance the shift of surplus acreage from the great export crops into feed.

A great many people argue that the main drift of the farm program should be to encourage an increased animal agriculture—that is, an agriculture which centers increasing attention on meat, milk and poultry while at the same time reducing the resources devoted to the direct cash crops which are the chief sources of our surplus difficulties. We are moving in this direction at a rapid rate. Specifically, the production of livestock and livestock products in 1956 was 23% above the 1947–49 average, while crop production only increased 6% over this period.

This shift in agricultural production is also associated with the main shift in American food-consuming habits. From 1935–39 into 1956, for example, Americans increased their per capita consumption of meat, milk and eggs by over 100 pounds, retail weight basis—about 24 pounds for beef, 10 pounds for pork, 5.6 dozen eggs or the equivalent of about 10 pounds, 11 pounds of ready-to-cook chicken, 3 pounds of ready-to-cook turkey, and the net gain of 50 pounds of dairy products, excluding butter (the increase includes 2.5 pounds of cheese, over 8 pounds of ice cream, and about 44 pounds of fluid whole milk).

Over against this, consumption of other foods, chiefly potatoes and grain products, has declined by almost 100 pounds, including a 14-pound decline in cornmeal, a 39-pound decline in consumption of wheat flour, a 32-pound decline for potatoes, and a 12-pound decline for sweet potatoes. Potatoes and grains have given way to livestock products—meat, eggs, milk.

To complete the picture there have been some offsetting shifts in the consumption of fresh versus processed fruits and vegetables, yielding some net gain in consumption rates; while the fat content of fats and oils, including butter, is almost the same now as earlier, 44.6 pounds per capita for 1956 as compared with 45.4 pounds average for 1935–39. Sugar consumption went down during the war period, is now back to almost exactly the 1935–39 level.

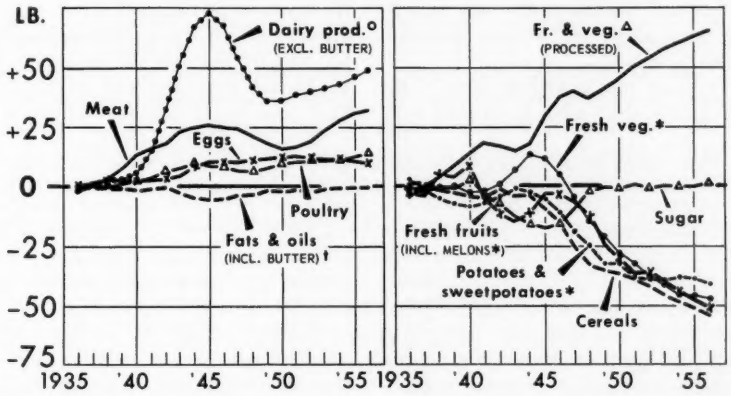

FIG. 2. Changes in food consumption—from 1935–39 average per capita. Variations in retail weight; civilian only; 3-year moving average centered. ○ Product weight except milk and cream content of ice cream. † Fat content. * Includes home garden produce. △ Includes frozen concentrated citrus juice on single strength basis. (U. S. Dept. of Agriculture.)

These data are shown in figure 2 using a 3-year moving average in place of each year's difference from the 1935–39 base. Moving averages smooth out some of the short-time variations and show trends more clearly. Table 1 shows average per capita food consumption, retail weight basis, in detail for 1935–39, 1947–49, 1955, 1956 and preliminary indications for 1957.

Although these comparisons go back to 1935–39, much the same situation exists if we measure from the more recent dates, say 1947–49. For example, since 1947–49, the two chief changes in the American diet as measured in terms of per capita disappearance are a 16-pound increase in the consumption of beef, 6 pounds of chicken, 2 pounds of turkey, and declines of 16 pounds of wheat flour, 15 pounds of potatoes, and 5 pounds of sweet potatoes. These shifts have meant not more pounds of food per capita, but rather a substantial improvement in the quality of the average American diet (measured either in terms of needed nutritional improvement, especially from 1935–39 into the mid-1940's or in terms of what people prefer to eat, income permitting).

Meanwhile, our increasing farm production has been supported by a veritable revolution in farming itself. Nutritionists and food processors quite often like to think of themselves as being expert technicians. Farmers too are expert technicians; over the last several years they have been producing more and more farm products from the same acreage of land and with fewer and fewer workers. Farm output has been increasing for the last several years at the same rate as population despite the fact that the emergency, war-time demand for export products has slacked off.

The next major point to which I want to call attention is that the products over retail food counters are not raw farm products as they leave the farm. Rather the actual foods which retail stores carry are made up of varying proportions of farm produce and of the many marketing and selling services which are necessary to put the particular product in the particular store at the particular time and the particular place that the American housewife or her husband, or the two of them together, want it.

When we buy beef or carrots or cake mix or canned soup or breakfast cereal the retail price must cover all of the costs involved in putting the finished article on the retail shelf. A sizeable part of the increase in the consumer food bill in recent years has come about because food processors and handlers are selling not only basic food products, but also increased services. Some people say it another way: the American housewife is today buying maid service bit by bit in the form of convenience foods and related services.

The fact that the consumer buys both food and associated marketing services as a unit accounts for the concern among farm people as to costs and margins for handling food and is also one of the two chief reasons why the economists' general rule that relative food expenditures tend to fall as family incomes rise has failed to work over the last several years. That is, with rising incomes American consumers have not only *a*) substantially increased the quality of

their diets but they are also at the same time *b*) purchasing more and more services and convenience with their food.

Suppose we now turn briefly to some of the national programs which have to do with food. We have a national School Lunch Program under which $100 million a year is available for cooperation with the States in the provision of hot school lunches for children of high school age or under. This program is further supplemented by *1*)

TABLE 1. PER CAPITA CONSUMPTION OF MAJOR FOOD COMMODITIES OR GROUPS, SELECTED PERIODS, AVERAGE 1935–39 AND 1947–49, 1955, 1956, PRELIMINARY INDICATIONS FOR 1957[a]

Commodity	Average 1935–39	Average 1947–49	1955	1956 Prelim.	Prelim. Indications for 1957
Meat, total	118.4	139.1	150.6	154.1	146.7
Beef	43.9	51.8	64.8	67.4	64
Veal	7.4	8.8	8.6	8.6	8.6
Lamb and mutton	6.1	4.3	4.1	4.0	3.8
Pork (excluding lard)	52.5	63.6	62.1	62.9	59.5
Edible offal	8.5	10.6	11.0	11.2	10.8
Fish, total (edible weight)	11.0	10.5	10.2	10.1	10
Poultry products					
Chicken (ready-to-cook)	13.4	18.7	21.4	24.3	24.7
Turkey (ready-to-cook)	2.2	3.3	5.0	5.1	6.0
Eggs (number)	291	373	360	358	345
Dairy products, exclud. butter[b]	376	418	423	426	427
Fluid whole milk	264	299	305	308	309
Ice cream	9.9	18.7	18.0	18.3	18.7
Cheese	5.6	7.0	7.9	8.1	8.1
Condensed and evap. milk	16.8	20.1	16.2	15.6	15.8
Fats and oils, total (fat cont.)	45.4	42.4	45.5	44.6	45.2
Butter	17.0	10.6	9.0	8.7	8.8
Margarine	2.9	5.6	8.1	8.2	8.2
Lard	11.0	12.4	10.1	9.9	10.0
Shortening	11.8	9.6	11.5	10.9	11.0
Other edible fats and oils	6.5	7.3	10.1	10.1	10.5
Fruits					
Fresh, excluding melons	139.6	130.6	96.0	96.2	93.6
Melons[c]	37.3	33.5	31.9	29.5	29.4
Canned fruit and juice	18.9	24.8	35.3	34.5	34.4
Frozen fruit and juice	.8	3.2	8.7	8.8	9.2
Vegetables					
Fresh, excluding melons[c]	198.0	186.2	149.4	151.7	151
Canned	30.1	39.2	43.8	44.3	43
Frozen	.4[d]	2.9	6.6	7.3	7.6
Potatoes[c]	128	111	102	96	98
Sweet potatoes[c]	19.1	11.5	8.0	6.9	5.7
Sugar and sirups					
Sugar (refined)	97.4	95.1	97.6	97.7	97.7
Sirups (including honey)	13.5	14.6	11.7	11.7	11.7
Grain products					
Cornmeal	23.1	12.8	9.2	9.0	9.0
Wheat flour[e]	160	137	123	121	119
Rice, milled	5.8	4.9	5.4	5.3	5.3
Beverages					
Coffee, roasted	11.8	15.3	12.9	13.2	13.2
Tea	.67	.58	.64	.61	.60
Cocoa[f]	3.2	3.0	2.8	2.9	3.0

[a] Retail weight, in pounds. Represents weight of food as usually purchased in retail grocery stores. Ingredients of bakery products and other mixed food items are shown in their primary food groups. Quantity in pounds except for eggs which are stated in number.

[b] Sum of individual products. Includes milk and cream used in ice cream.

[c] Includes quantities produced in home gardens.

[d] Average 1937–39. Data prior to 1937 are not available.

[e] Includes white, whole wheat and semolina flour. [f] Chocolate liquor equivalent.

Population estimates used to obtain per capita consumption figures are official Census estimates of civilian population adjusted for military personnel eating out of civilian supplies.

an authorization of $75 million for a Special Milk Program which assists in increasing the consumption of milk and *2*) the donation of various surplus foods to the School Lunch Program—for example, during the current school year, this surplus list has included beans, butter, cheese, dry milk (for cooking), rice, pork, hamburger, shell eggs, turkey, and in some cases wheat flour and cornmeal, as well as *3*) the expenditures of school children themselves for their lunches along with sums appropriated by the States or school districts to help run the program. This is one of the best-received of the Government programs. The total cost or outlay, including Federal expenditures, donated commodities, State and local funds, and lunch payments of the children themselves during the current year will run about $850 million and cover about 12 million school children.

We also have a program which allows the donation of surplus agricultural commodities to charitable institutions and to needy people. In case of donations to needy people the State government must accept the responsibility *a*) for identifying and certifying families which fall within the needy category and *b*) for accepting in carload lots the appropriate surplus food at terminal points and taking care of the distribution task. During the current fiscal year, we have been distributing to charitable institutions and needy people chiefly rice, beans, cheese, dry milk, cornmeal and wheat flour. The total value of domestic donations will probably run something under $250 million, supply some quantities of food to nearly 3½ million needy persons in 39 States and in Alaska and Puerto Rico. Perhaps I should add that surplus agricultural commodities are also made available to needy people in friendly foreign countries, through appropriate charitable agencies—after priority has been given to requests for our own School Lunch Program, charitable institutions and needy people. Foreign donations, chiefly of dry skim milk, cheese, cornmeal, rice and wheat flour, may run over $250 million or more in the fiscal year ending June 30, 1957.

I think when you look at the character and nature of the acreage-allotment, marketing-quota, price-support, and Soil-Bank programs and when you consider that the total value of all the commodities and funds going into the School Lunch and surplus distribution programs within the United States only runs about $1 billion, you begin to understand my earlier statement that what we are chiefly concerned with is the commerical market for food and the day-to-day, season-to-season, and year-to-year influences which affect it.

At the same time, when you look at our farmers' ability to produce, at the great flood of farm products which their farms turn out each year, it is easy to understand why American farmers and their leaders are so much interested in today's food market. Farmers and those who work with them are not arguing that most of us should eat more food but that we should eat better food—better as measured against both consumer preferences and the nutritional needs of our time. This certainly offers a challenge to and raises some real questions for, those of you working in nutrition education. Most Americans now have the means and food at hand to eat a good diet. But some of us eat the wrong 'mix' no matter how well off we are.

There is one final note or item that may be of interest. As nutritionists, I am sure you are concerned not only with nutrition in the United States but also with nutritional problems wherever they may be found. During World War II, substantial encouragement was given to the development of dry skim milk plants in our midwestern States. We not only continue to have the plants to produce dry milk, chiefly milk solids non-fat, but it is also a fact that an increasing number of farmers want to sell all of their milk, both the fat and nonfat portion, rather than simply selling the butterfat and using the skim milk for livestock feed.

American dry skim milk, or if you prefer the official or technical name, 'nonfat milk solids', is a product which not only has outstanding nutritional value and surprising keeping qualities but which also seems to be acceptable to hungry people the world over. It has supplied the base for supplemental feeding programs of one kind or another in many nations over the world. We are still currently supplying this product on a practically cost-free basis to charitable agencies engaged in feeding needy people in friendly countries and to UNICEF (United Nations Children's Fund), as well as making low-cost concessional sales for school lunch purposes to such countries as Japan, Brazil and Israel. Here is a product which has revolutionized the feeding of children in many areas and has set many of our foreign friends to considering ways and means by which they might develop their own sources of milk or equivalent supplementary feeding material.

NEW DEVELOPMENTS IN FOOD PROCESSING WITH NUTRITIONAL IMPLICATIONS

H. E. ROBINSON

From Swift & Company, Chicago, Illinois

THE 20 YEARS just passed have seen many radically new food products introduced for public use and a substantial number of new food processes have been inaugurated in industry. It would seem probable that the overall nutritional implications of modern food processing are very much to the good. Some consideration will be given to each of several individual food fields.

The program for enrichment of bread, flour and cereal products is still in the modern era. This restoration of important nutrients lost in processing has undoubtedly had a very positively good nutritional effect for the American public. The basic policy of the enrichment program, that of restoring lost nutrients, rather than to attempt the addition of new nutrients or unusual amounts of them to individual foods has become almost an axiom in the food industry.

SPECIAL PURPOSE FOODS

New special purpose foods which are low in calories, principally because of the low fat content, and are high in proteins, vitamins and minerals are now being successfully test-marketed in the United States. These foods are designed for appetite appeal and satiety value and are useful particularly for diabetics, cardiac patients, hypertensives, weight reduction programs and for expectant mothers. Laboratory data clearly demonstrate that controlled institutional cookery of the special purpose and baby foods tends to preserve more of the original nutritive content of the products than has been the case in hit-or-miss home preparations of the past.

Special purpose foods are foods designed to meet unique and specific physiological requirements. Modern food processing permits the manufacture of special purpose foods that cannot conveniently be prepared in the home and, in many cases, their preparation is so complex that home preparation is impossible.

One of the largest areas of need for special purpose foods is in the field of pediatrics. Here we have an organism which requires special consideration, both in the physical properties and nutritional composition of the diet due to the organism's immaturity.

The most revolutionary and nutritionally logical change that has been made in the infant feeding program in the last few years has been the adoption of the early feeding of solid foods. Forty years ago only the most progressive of physicians would have offered an infant solid food during the first year of life. Twenty years ago, a few of the bolder practitioners were giving their patients cereals at the age of 6 or 7 months. Now we find that solids are being offered at only a few weeks of age, sometimes before the baby leaves the hospital. Our experience has been that even premature babies as young as one week of age can digest and utilize the nutrients in strained meat.

The canned foods industry has made rapid strides in the development of vegetables and fruits for infants and children since this field was first opened in the 1920's. The commercially prepared vegetables and fruits may be said to be more effective when used for infants than the home-cooked product. There is constancy in the product, it is more finely strained, the end product is more uniform in vitamin and mineral content and its precooked state assures the consumer the uniformity of the mineral and vitamin content without the overcooking deterioration which may be obtained in domestic preparation. A high nutrient level is also maintained by the selection of the raw materials. A good example of the effect of selection of raw materials on the final product is in orange juice products. The vitamin C content of oranges varies considerably and at times the fresh oranges purchased on the open market in Chicago have ascorbic acid values as low as 14.5 mg/100 cc. By picking the oranges at the proper time and by canning the orange juice at the site of the orange grove, some manufacturers of orange juice for babies have been able to maintain an ascorbic acid level as high as 58 to 62 mg of vitamin C/100 cc and essentially guarantee a level of about 40 mg/100 cc.

Eggs have always been popular as a source of

iron, protein, vitamins A and D and the B vitamins for infants. Because many infants are allergic to egg white, generally only the egg yolk is fed. This presents no particular nutritional hardship since most of the nutrients of egg are concentrated in the yolk portion. Currently, fluid egg yolk preparations are available for infants. Tests have shown that strained egg yolks have improved acceptability over the hard-boiled egg yolks usually offered to infants and also have the advantage of uniformity. More recently, these have been flavored with bacon so that now even the youngest infant can enjoy that old American favorite, 'Bacon and Eggs'.

A late arrival on the field of solid food for infants is meat. Although it had its beginning only ten years ago, it is now a well-accepted item in the infant diet. Before its inception in 1946, there were a few progressive pediatricians recommending meat for their infant patients. In most cases, the only meat an infant received was bacon and this was given not so much for its nutritional value as for its chewing properties. Apparently, its salty flavor and softness soothed the infant's gums as he was teething. Marriott and Jeans stated that 'meat properly prepared could be fed at any age'. However, the home preparation of meat was such a task that very few infants received this nutritious food in their diet.

By carefully trimming meat of fibrous connective tissue and comminuting the meat to a custard-like consistency, it was possible to prepare commercially a satisfactory product for infant feeding. In view of the difficulties that some infants have in tolerating fat, the fat was carefully removed so as to keep its content at a minimum. The high quality protein of meat offered at the time the infant needs from three to four times as much as the adult makes a significant contribution to the infant's dietary. Meat also supplies essential B vitamins and minerals, particularly iron. The theoretical nutritional advantages of meat have been confirmed by clinical studies conducted at various universities and hospitals. Today's human babies are the best-fed organisms in all of nature. It is too bad that we cannot say the same for the balance of the growing period.

CONVENIENCE FOODS

Modern food processing has brought about the introduction of a vast number of 'convenience foods'. These convenience foods include partially prepared and an ever-increasing number of fully cooked foods. The food industry may take credit for this advancement, of course, but the impetus behind this progress might well be attributed to the American homemaker.

Today there are 22,000,000 women who work outside the home for pay. There are countless women who volunteer hours of work outside the home on worthwhile projects for the betterment of our communities and mankind. This means women have less time to spend cooking than they did in former years. Only 4% of the families in the United States have maids and much of this help is just part-time. Therefore, homemakers in our country have become more and more conscious of the time and labor saved by new convenience foods. They welcome each new food item that makes it possible to serve good meals that require little or no preparation time. As a result of these new foods, today the average homemaker spends 2½ to 3 hr., or less, a day in her kitchen, whereas 30 years ago she spent at least twice that time.

It is no doubt true that modern canned and frozen foods have been so perfected that the nutritional quality of the food may be better than that of the same food purchased fresh and prepared in the home. Production knowledge of both the canned and frozen food industries shows that foods are processed at exactly the right stage of maturity and quickly packed or frozen under scientific controlled conditions so as to retain the full natural flavor and maximum nutritive value which is a factor that cannot be over-emphasized. Modern packaging that seals in the goodness maintains this on-the-spot freshness. And, in the case of frozen foods, proper storage continues to maintain this freshness at a stable and high quality standard.

Foods high in nutritive content are now available to the busy homemaker in cans, in foil and parchment wrappers, in foil trays and casserole-type dishes—canned and frozen, partially and fully cooked—for quick-to-prepare-and-serve meals that are tasty and eye-appealing too. Besides the wide variety of fruits and vegetables we can now add a host of other convenience foods that mean meals in minutes. There are 'brown 'n serve' sausages that are ready for the table in 3 minutes' time; frozen chicken à la king, salmon loaves, spinach soufflés, stuffed green peppers and other prepared dishes that

just need to be heated; frozen baked waffles and pancakes that are ready to eat after a quick heating in the pop-up toaster; frozen meat and vegetable pies ready to bake and serve; hard, soft and sweet rolls ready to brown and serve; and also the complete meals in trays that after a time in the oven are table-ready. With the addition of a beverage and the most convenient food of all—ice cream—these tray meals are nutritionally complete. There are the canned dietetic foods, salt and sugar free, that are convenient for those on prescribed diets. There are the fruits, vegetables, puddings and meats in cans and jars for the infants and juniors. And last, but not least, there are the complete diet foods in cans or in packaged meal form for the pets in the family.

Modern food processing, stimulated by the needs of the modern homemaker, is meeting the demands of the times. Capturing the original goodness of the raw product, processing under scientific conditions, packaging to maintain the freshness, and offering a wide variety of flavorful, attractive foods—the food industries are supplying more nutrients.

DEHYDRATED FOODS

Dehydration is one of the oldest methods of food preservation, yet not until recent years have advances been made which have greatly improved the quality of many of these dehydrated products.

In general, the methods now employed for the dehydration of fruits, vegetables and milk conserve the nutritive value with the possible exception of vitamin C. Sulfuring fruits and vegetables during preparation for drying increases the vitamin C retention, but destroys much of the thiamine. Scalding of the vegetables prior to the dehydration destroys enzymes and preserves the nutritive value, enhances palatability and improves overall quality. Scalding also permits maintenance of quality during storage.

Storage losses of carotene and ascorbic acid are apparently greater than those of the other vitamins. A moisture of below 1% in many dehydrated items must be obtained in order to preserve flavor, color and vitamins for any length of time. Products packed under carbon dioxide or nitrogen also have improved keeping qualities.

The list of satisfactory dehydrated fruits and vegetables now includes apples, orange powder, grapefruit juice, tomato powder, potato granules, dry potatoes, onions, peppers, green beans and sweet corn.

Recent advances have been made in the technology of drying milk that improve the nutritive quality of this product. Lower drying temperature, consumer-size packages for dried skim milk and improved stability of added vitamins A and D have all contributed greatly to the improved dried skim milk and dried whole milk.

The practice of removing glucose during recent years from whole eggs, whites and yolks, has likewise improved these products. Dehydrated whites are now used in dried angel food cake mixes which have excellent acceptance. Removal of glucose from whole eggs permits them to be held for longer periods of time without impairment of quality.

Although freeze-drying today has limited use commercially, it appears that this method of drying will cause less destruction of nutrients than any of the other methods.

Advances in dehydration have been brought about primarily by improved techniques as *1*) sulfuring *2*) reduction to a very low moisture content by in-package desiccation *3*) use of low temperatures for dehydration and *4*) improved packages. More dehydrated foods will be sold as their quality improves. They should offer good retention of nutritive values.

FATS AND OILS

Crude vegetable oils and meat fats contain 96–99% glycerides. The remainder consists of free fatty acids, phospholipids, sterols, pigments, vitamins and fragments of a variety of resins and gums. Normal commercial processes of water-washing, alkali washing and decolorizing the vegetable oils remove almost all of the non-glyceride substances. There is considerable loss of tocopherol, vitamin A, phospholipids and sterols. These may represent a nutritional loss; however, the removal of gossypol from cottonseed oil is a nutritional gain. The hydrogenation process causes several changes; among these are the reduction of the unsaturation of carentoid pigments, the addition of hydrogen to the fatty acids of the glycerides, the migration of double bonds and the conversion to 'trans' isomers. The nutritive implications in such losses of essential fatty acids are not known despite some recent theoretical discussions of potential metabolic

involvement of so-called unnatural fats. We do not here wish to enter into a discussion of the fats versus the atherosclerosis question. Suffice it to say that individual fats and oils have received a variety of publicity in the public press and elsewhere as to a possible relationship to heart disease. That segment of the food industry which is represented in this field is anxious to learn the truth and is supporting wholeheartedly many strong programs in the metabolism of fats. In the meantime, the industry hopes that unwarranted conclusions will not be drawn until a sufficient amount of data has been accumulated to be reasonably conclusive.

Investigators in several laboratories have demonstrated that the nutritive value of fats may be decreased by severe heating, by oxidation or by heating and oxidation under laboratory conditions. Based on these observations it has been suggested that similar changes may occur in commercial frying operations. There is no question that severe heating and/or oxidation causes changes in fats that result in impaired growth and some tissue changes in animals to which they are fed. However, the conditions of commercial usage differ so widely from those of laboratory testing that the validity of extrapolation is extremely questionable. Our laboratory recently evaluated 34 samples of fats obtained from various commercial frying operations. Even the most severely used samples showed only slight decreases in calorie availability and nutritive value. This indicates that normal conditions of commercial usage have little or no effect on the nutritive value of the fats.

RADIATION PRESERVATION

Radiation preservation is a newcomer to the food field. This process employs ionizing radiation—specifically, electron beams or gamma rays—to destroy food spoilage organisms and, thereby, to secure preservation of the food in question. At the present, this process is still in the development stage, being held up largely by problems relating to radiation-induced changes of an organoleptic nature, such as alteration of flavor, appearance, etc. There exists also the problem of inactivation of enzymes present in certain foods, which could cause undesirable changes on storage. It is current thinking that the inactivation of such enzymes will be accomplished by procedures in addition to irradiation, since the amount of irradiation needed for inactivation is considerably larger than that needed for bacterial destruction. If such problems can be solved radiation preservation offers many intriguing possibilities for the improvement of foods, such as freedom to prepare canned items having shelf stability with any heating being determined by culinary considerations rather than sterilization requirements, extension of product life through the use of a 'pasteurizing' amount of radiation, etc. Such possibilities, if accomplished, could very well cause irradiation to take a place among the currently standard food preservation methods.

One of the first considerations of any new food processing operation is that of its influence on nutritive value. In the radiation preservation process it appears that as many as 5 million rads may be required to assure a sterile product. This actually is a small amount of energy, about 10 Cal/gm. One might expect that such a small amount of energy would have only a minor effect on the nutritive value of a food, unless it were highly selective and operated in a preferential way on certain nutritionally important food components. The very complexity of the constitution of foods plus the accepted mechanism of the action of ionizing radiation argues against this.

That radiation does not greatly affect the wholesomeness and nutritive value of meats has been demonstrated by several long-term experiments, including one in our own laboratories. These studies have shown that the growth, reproduction, health and longevity of experimental animals is not significantly altered by the feeding of high dietary levels of irradiated meats.

Time does not permit an evaluation of every field of changing processes in the food industry. It does seem reasonable to say that the emphasis on continuous processing and automation will steadily reduce cooking times and temperatures to the overall benefit of retention of nutrients in the product. The present pattern of producing appetizing, eye-appealing and scientifically packaged 'convenience' foods will continue and is a positive aid to good nutrition

FOOD AND NUTRIENT CONSUMPTION TRENDS AND CONSUMER PROBLEMS

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WE HAVE HERE in the United States an excellent opportunity to choose the kind, the quantity and the form of our food. Our markets offer a wide variety and supplies of food are generous. This favorable situation gives rise to the question—Are we making good use of our opportunity for high levels of nutrition? Your Committee must have had some such question in mind when they asked me to discuss trends in our consumption of food and some of their nutritional implications.

My discussion today is based on figures from surveys of household food consumption made by the U.S. Department of Agriculture. The latest one, made in the spring of 1955, covered a national sample of 6000 families. It provides data on the quantities brought into the kitchen of some 200 or more food items—classified by income, region and degree of urbanization. Ten volumes of basic data report this 1955 survey, providing figures on expenditures for food, consumption and nutritive content of diets. From this vast array I have chosen a few figures that may be of special interest to you.

Something of the kind and average quantity of foods used in this country is suggested by the fact that this supply could provide average diets that might be described about like this: *1)* Three to four servings of vegetables and fruit a person a day, including dark green and deep yellow vegetables once or twice a week, and citrus fruit 4 or 5 times a week; *2)* the equivalent of 2 to 3 cups of milk each day; *3)* an egg and 1 or 2 servings of meat, poultry or fish each day; *4)* bread or other grain products at each meal.

Table 1 shows the estimated nutritive content of this assortment and these quantities of foods, in terms of calories and nine nutrients. Many additional analyses of the original data can and should be made for specific nutritional purposes.

For each nutrient shown the amount is considerably larger than the recommended dietary allowances of the National Research Council's Food and Nutrition Board. But the data refer to the nutrients in the amounts of food that come into household kitchens for consumption. Of these amounts an unknown portion is discarded either as plate waste or in the kitchen. Nevertheless, these high *average* figures point to the fact that the great majority of families in this country could be well fed.

Table 2 shows, however, a need for improved diets. The first column shows the proportion of families whose diets failed to provide in full the recommended allowances of NRC for each specific nutrient; the second, the proportion that had diets, failing to provide as much as two-thirds of these allowances. Our data are reported not only in terms of averages but also in terms of the proportion of families with diets providing different levels of nutrients. In this discussion I am using the NRC diet allowances as points of reference. You may use others if you choose.

Of protein, diets of only 8% failed to provide NRC allowances in full, and those of only a very few failed to provide at least two-thirds of the protein allowances. It is obvious that more families fell short—as compared to NRC allowances—in calcium and ascorbic acid than in other nutrients shown. Smaller but substantial proportions had diets that furnished less than recommended amounts of vitamin A, thiamine and riboflavin.

We do not, of course, conclude that all families whose food provides less than the NRC allowances are poorly fed or subject to malnutrition; the allowances represent dietary guides and aim to provide a considerable margin of safety over minimal needs of the average person.

Diets in this country have been greatly improved since the large-scale survey of 1936, made as we were emerging from an economic depression. Then, about one-third of the families in this country had diets that were classed as 'poor'. Today, if judged by the standards used in that earlier period, probably not more than one-tenth of the population would have diets rated 'poor'.

The dietary improvement of the past 20 years has been a result of a combination of factors.

TABLE 1. NUTRITIVE CONTENT OF FOODS AVAILABLE FOR CONSUMPTION: PER PERSON PER DAY, SPRING 1955

Food energy	Cal.	3,200	Vitamin A value	IU	8,540
Protein	gm	103	Thiamine	mg	1.6
Fat	gm	155	Riboflavin	mg	2.3
Calcium	gm	1.2	Niacin	mg	19
Iron	mg	18	Ascorbic acid	mg	106

We have enjoyed economic conditions under which an increasing proportion of people have been able to have the kinds of food they want. Average real income (income after adjustment for increase in prices) has increased with the increases proportionally greatest among families at the lower end of the income scale. Our market supplies of food have been ample, varied and of high quality. We have had continuing emphasis on research and education in nutrition. And finally, enrichment of white flour and bread has been widely practiced since the early 1940's.

The nutrients showing the greatest per-capita increases since 1936 are iron and the three B-vitamins that are added to grain products as ingredients for enrichment. As a result also of higher consumption of milk and meat, not only niacin and riboflavin but, in addition, calcium and protein have increased considerably since 1936.

Most of this dietary improvement, however, seems to have taken place between the mid-thirties and the early postwar period, and relatively little since 1948. This is a point to which nutritionists should give thought.

For protein, somewhat more families met NRC allowances in 1955 than in 1948. This reflects increased consumption of meat, poultry and fish. In the spring of 1955, families had an average of 4⅓ pounds per person per week, compared with a little more than 3 pounds for the same season in 1948. Approximately the same proportion of families had diets that furnished recommended amounts of calcium, vitamin A, thiamine and riboflavin—nutrients often in shorter than desirable supply. Somewhat fewer had diets providing recommended levels of ascorbic acid in 1955 than in 1948. The pattern of consumption of vegetables and fruit put a little less emphasis in 1955 than in 1948 on the dark green and deep yellow vegetables and on the vitamin C-rich fruits.

With the United States covering so large a geographic area we would expect to find regional variation in food patterns. In this survey four broad regions were identified—Northeast, North Central, West and South. Under economic conditions prevailing, families in regions of the North and West in 1955 spent more for food than did those located in the South. Higher average levels of milk and lean meat consumption in the North and West account for the lower proportion of families there than in the South with diets falling short of NRC allowances in protein, and higher consumption of milk is reflected in lower percentages of families short in calcium and in riboflavin. With greater consumption of vegetables and fruits of all kinds, fewer families in the North and West were short in vitamins A and C. Consumption of separated fats, sugars and grain products was higher in the South than in the North and West, however, reflecting both lower expenditures for food, and a higher proportion of the population living on farms in the South.

TABLE 2. NEED FOR IMPROVED DIETS, 1955

Nutrient	Percentage of Families with Diets Meeting NRC Allowance	
	Less than 3/3	Less than 2/3
Protein	8	1
Calcium	29	8
Vitamin A value	16	6
Thiamine	17	3
Riboflavin	19	3
Niacin	7	1
Ascorbic acid	25	10

These data come from studies covering only the spring season. For urban diets the information we have leads us to think that nutritive content in the spring is closer to the year's average than in any of the other three seasons; this may not be true for farm families.

Next we come to a matter of wide current interest: the nature and quantity of fat in modern diets.

Several years ago life insurance companies, from an analysis of their statistics, brought to public attention the association of obesity with high death rates from a number of diseases, including cardiovascular disease. Since then, a number of scattered studies made among different racial and socio-economic groups in various parts of the world have associated richness of diets in fat with elevated levels of serum chol-

TABLE 3. DEATH RATES, ARTERIOSCLEROTIC HEART DISEASE AND POPULATION IN CITIES, 1950

	North-east	North Central	West	South
Death rates (420)/ 100,000	263	203	217	169
Pop. in towns and cities of 2,500 and over, %	79	64	70	59
Percentage of U. S. Totals				
Death rates (420)	123	95	102	80
Pop. in towns and cities of 2,500 and over	124	100	109	76

TABLE 4. FAT BROUGHT INTO KITCHENS: PER PERSON PER DAY, SPRING 1955

	North-east	North Central	West	South
Total fat, gm	146	160	164	156
Saturated fats, gm	63	69	68	63
Oleic acid, gm	60	68	69	70
Linoleic acid, gm	16	16	18	17
Iodine value of fat	61	61	63	65
Total Calories, in 100's	29	33	33	33
Cal. from fat, %	45	44	45	42
Cal. from satur. fat, %	19	19	19	17
Oleic plus linoleic acids, gm: Cal. from satur. fat, %	4.0	4.4	4.6	5.1
Linoleic acid, gm: Cal. from satur. fat, %	0.8	0.8	1.0	1.0

esterol, and limited data for these groups with high serum cholesterol tended to point to higher death rates from coronory heart disease and upon autopsy, greater incidence of atherosclerosis.

Controlled laboratory and clinical studies have demonstrated that marked shifts in the nature of dietary fat can effect changes in serum cholesterol levels of adults—in general, the use of fats rich in certain unsaturated fatty acids can reduce levels of serum cholesterol, as contrasted with fats that are rich in saturated fatty acids.

In the fall 1956, the U.S. Public Health Service released reports by State and Census regions of death rates from arteriosclerotic heart disease, including coronary (No. 420 on the international list of causes of death). It seemed of interest to learn whether average figures from our survey data on the quantity or kind of dietary fat would vary from region to region with death rates from this cause.

Table 3 shows the age-adjusted figures on death rates provided by U.S. Public Health Service for the four groups of States or regions included in our dietary survey. Clearly, they are much higher in the Northeast than in the South and intermediate for the other two regions. Also shown is the proportion of these regional populations living in towns or cities of 2500 and over.

The lower section expresses these figures as percentages of corresponding values for the country as a whole. Thus, in the Northeast, the death rate was 23% higher than for the country as a whole, and the proportion of people living in towns or cities is 24% higher. In the South, the death rate is only 80% of that for the country as a whole, and the proportion of people that live in cities is 76% of the average. The difference in urbanization between the Northeast and the South would be much more pronounced if there were only to be considered those living in large cities—cities of 100,000 and over.

The parallelism between death rates and urbanization may be only an artifact such as can result when the variables in a correlation are descriptive properties of groups of people rather than of individuals. Moreover, the adequacy of the reporting of cause of death probably differs from region to region, influenced no doubt, in part, by the presence in cities of specialized medical personnel and facilities. On the other hand, the parallelism may suggest that for urban dwellers the stresses of living—perhaps including overeating—are less counterbalanced by vigorous use of the body's large muscles than for those living in the open country. Thus, mode of life may be a factor in death rates from this disease.

To return to the dietary data, outstanding differences among the regions were the higher percentages in the three regions of the North and West than in the South of total fat derived from dairy products and from beef, veal and lamb, and the lower percentage from pork and from lard. The fat of milk and beef, as is well known, is higher in saturated fatty acids than is that of pork. Poultry, eggs, fish, cooking oils and salad dressings—some of which are important for unsaturated fatty acids—each furnished relatively small proportions of the total dietary fat. Margarine and shortenings—the chief hydrogenated fats—provided 14% of the total

fat in the West and South, somewhat more than in the other two regions. The share of dietary fat contributed by other foods was about the same in each of the four regions.

Table 4 shows the quantity of fat brought into kitchens per person per day, and something of the nature of the dietary fat.

The total fat used was lower in the Northeast than in the other three regions, with figures highest for the North Central region and the West. Of course, not all fat brought into the household is actually eaten, but we have no good basis for estimating the loss.

The amount of saturated fat used was about the same in the Northeast and the South, but it represented 43% of the total fat in the Northeast and only 40% in the South. On the other hand, the combined quantities of oleic and linoleic acids—the chief unsaturated fatty acids found in foods—were considerably less in the Northeast than in the South. The iodine value of dietary fat was estimated to be lower in the two Northern regions than in the West and South.

Calorie levels were lower in the Northeast than in the other three regions—2900 calories/person/day as compared to 3300. The proportion of total calories derived from fat was higher in the three regions of the North and West than in the South. This also was true for saturated fat.

Whether oleic and linoleic acids are combined, or only linoletic acid is considered, the ratio between the quantities of these unsaturated fatty acids and the richness of diet in saturated fats (expressed as percentage of calories from saturated fat) is considerably lower for the Northeast than for the South.

Between the Northeast and the South the ratios differed by 20%. Table 3 shows that death rates from arteriosclerotic heart disease were highest in the Northeast and lowest in the South—the death rates for the two regions differ by more than 50%.

The *direction* of the differences between the Northeast and the South in kind of fat is such that one might perhaps expect higher levels of serum cholesterol among adults living in the Northeast than in the South. Whether the *amount* of the difference is great enough to be thus reflected—even if persisted in for decades—can only be determined by research on this point. The difference in amount is considerably less than is required to modify serum cholesterol levels under short-term experimental conditions.

Table 5. Need for changed food habits, 1955

Nutrient	Percentage of Families with Diets not Meeting NRC Allowances	
	All families	Families in top third of income scale
Protein	8	3
Calcium	29	23
Vitamin A value	16	10
Thiamine	17	16
Riboflavin	19	13
Niacin	7	4
Ascorbic acid	25	6

Undue emphasis should not be given to these regional differences in fat inasmuch as they represent only rough approximations of both the use and the composition of the fat, and the statistical significance of differences in use has not yet been determined.

What the minimum requirements for unsaturated fatty acids are in relation to saturated fats under differing nutritional and other environmental factors remains to be determined. The relative effectiveness of the different unsaturated fatty acids for different metabolic functions also needs further study. Moreover, many aspects of diet other than the kind and amount of fat also are known to influence fat metabolism—the level of protein and of certain amino acids, of vitamins, minerals and carbohydrates. The practical importance of each of these factors is not yet known, but their interrelations in present-day diets should be explored.

The final table, table 5, summarizes the extent to which we must depend for further diet improvement on forces that change food habits, such as education, and the extent to which we can depend on improved economic situations for better diets.

For each of seven nutrients is shown the proportion of households failing for any reason to have diets that provide in full the allowances recommended by the National Research Council. (These figures repeat those of the second table.) Also shown is the proportion of families in the top third of the income scale whose diets fell short—families for whom, surely, economic considerations were not the chief barrier.

The table also shows that the various nu-

trients are affected differently by changes in the economic situation. In this country, as people have more money to spend for food, they are likely to buy more meat. In consequence, if you accept NRC allowances as a suitable point of reference, a much smaller proportion of families in the upper income third are short in protein or niacin than is true for all families the country over. In a period of prosperity, then, a nutrition education program might need to put less emphasis on food sources of these nutrients than on some others.

Continued prosperity could also mean that more families would add more milk and fruits and vegetables to their diets. But, as the table shows, even under favorable economic conditions, good sources of calcium and ascorbic acid would probably still need to be emphasized in nutrition education programs.

Thiamine also would need emphasis in a nutrition program for a prospering economy. High income families are likely to shift away from the grain products and pork, and the foods chosen to replace them may not be equally good as sources of thiamine.

The wide opportunity for choice that persons now have because of larger incomes and the greater variety of foods on the market provides an increasing opportunity for improving and extending consumer education in nutrition. Families with limited purchasing power need help from nutrition education, but this need exists also among families in every income bracket. The proportion of families in the top income third whose diets failed to meet recommended nutrient allowances indicates that we face a continuing and important task in effective nutrition education. This situation is a real challenge to us all.

MEDICAL AND PUBLIC HEALTH ASPECTS OF SOME RECENT DEVELOPMENTS IN NUTRITION AND FOOD TECHNOLOGY[1]

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WE ARE LIVING IN AN AGE of great change, the most revolutionary period in all history. Change is evident in all human activities; it has been most rapid and more fundamental, perhaps, in the physical and biological sciences. It has had a tremendous impact on industry and agriculture, leading to new patterns of living for the individual and the community. It has greatly improved the public health and prolonged the span of human life.

The results of scientific and technological advances are shown even in the food we eat. In my presentation I shall cover these developments under five general categories, some of which will be discussed very briefly, others at considerable length.

1. NUTRIENTS AND DRUGS

Of the recent advances in nutrition which have affected public health, perhaps the best known and appreciated are the isolation, the large-scale manufacture and the application of vitamins hormones and antibiotics. The tremendous expansion in manufacture is evident from the data in table 1. These substances are supplements and drugs, having either direct action on metabolism and growth or indirect effects through control of bacterial growth and infections.

The vitamins, the wonder drugs of yesterday, are freely available today in the form of tablets and capsules. In most states they are added to milk, margarine, and to cereals and cereal products in accordance with their laws and public health regulations. They are added to many supplementary and therapeutic foods. This widespread use has led to the virtual disappearance of the classical vitamin deficiency diseases as a major public health problem. Thus, although the incidence of pellagra and beri-beri heart disease formerly may have been high among low-income groups, particularly among alcoholics (1–3), such incidence of primary avitaminoses has become uncommon since initiation of the nutritional enrichment program in the early 1940's. This is illustrated, for example, in a study at Cook County Hospital, Chicago, in 1946, in which I participated (4), and in a survey by the U. S. Army Medical Nutrition Laboratory (5) among inmates on admission to the House of Correction, Chicago, in 1948 and 1949. This is further shown by the mortality statistics in the United States (6) for the years from 1935 to 1955 (table 2). Such statistics have obvious limitations, which cannot be indicated in this discussion.

Vitamins are assuming increasing importance in animal feeding; in fact, more of the vitamin manufacture is being used for this purpose than for human nutrition and medicine. This application to food production has great economic importance.

The hormones are perhaps best known for their therapeutic use in human diseases such as diabetes, thyroid diseases, arthritis, allergies and so forth. In addition, they (or hormone-like substances, or compounds which affect the endocrine glands) have tremendous importance in meat production. For example, estrogens or diethyl stilbestrol are being used for improving feed efficiency and carcass quality in beef and poultry. Although the applications to animal feeding are still under intensive study, a large percentage of the farm animals coming to market have received hormones (primarily diethyl stilbestrol) either in feed or in implants.

During the past 15 years, some 20 antibiotics with distinctive actions against pathogenic and saprophytic bacteria, and against yeasts and molds, have been isolated. Their uses have been intensively studied and widely applied. The search for newer antibiotics is continuing. The best known use is in the prevention and treatment of human and animal infectious diseases. Perhaps the greatest potential use is in animal production and in meat processing. In 1955, about one-fourth of the 2,092,000 pounds of antibiotics was used in animal feed supplements (table 1). Recently introduced applications, which already have wide industrial acceptance,

[1] The opinions expressed in this paper are those of the author, and do not necessarily represent those of any Governmental agency.

TABLE 1. PRODUCTION OF VITAMINS, HORMONES AND ANTIBIOTICS IN THE UNITED STATES FROM 1940 TO 1955

Substances	1940	1945	1950	1955
Ascorbic acids and salts	33.4	1307.1	1227.5	2354
Niacin	3.8	958.3	1447.6	2318
Pantothenic acid, Ca salts			155.4	521
Pyridoxine		2.7	17.5	30
Riboflavin		68.9	199.0	311
Thiamine		169.7	237.4	234
Vitamin A, alcohol and esters			95.3	170
Vitamin K		0.9		4
Vitamins, all other		63.5	72.9	164
Hormones, estrogenic		0.4*	2.7*	15†
Antibiotics for human and vet. use			852.9	1572‡
Antibiotics for animal feed supplements				520
Amino acids, all		176.0	926.1	1768

The results are expressed in thousands of pounds. The data are taken from Report of U. S. Tariff Commission, Synthetic Organic Chemicals, United States Production and Sales. Report nos. 148, 157, 173, 198.

* Diethyl stilbestrol.

† Includes all estrogenic and other steroid hormones.

‡ Includes 455,000 pounds of penicillin, 369,000 dihydrostreptomycin, 154,000 streptomycin, 15,000 neomycin base and 579,000 of all other antibiotics.

are in the processing of poultry and fish (7). In the feeding of farm animals, the tetracyclines appear to be the most effective antibiotics, according to stock feeders and animal husbandry men with whom I have talked. In cattle, the antibiotics, given in the feed, improve the daily gain from 0.1 to 0.5 lb., increase the food efficiency by 5 to 10%, enhance the carcass quality, are complementary and additive to stilbestrol and minimize the incidence of disease during shipment.

2. THERAPEUTIC AND SPECIAL FOODS; CORRECTIVE DIETARY SUPPLEMENTS

Research on therapeutic and special foods has been very active and diverse within recent years. The needs are great and the technologic advances have been rapid. Fairly acceptable protein concentrates which have an important place in therapeutic nutrition have been developed. Examples of such are casein, egg albumin and soy bean protein. They are used for high-protein feeding for nutritional rehabilitation in hospital cases and supplementation at home in special cases. But the cost is rather high, and the acceptability often is low. However, in our laboratory, it has been possible to prepare many food dishes with greater acceptability, with just as great increase of protein content, by using high protein foods such as eggs and milk solids, instead of protein concentrates (8).

The amino acids have equally great promise. The manufacturing costs have decreased rapidly and the various amino acids have become available in such large quantities that it is feasible, now, to consider their use for supplementation of marginal diets of some population groups (see table 1). In practice, their use presents many theoretical and technical difficulties. The addition of such protein-rich items as eggs and fat-free milk solids accomplishes much the same result as addition of specific amino acids. However, the amino acids should have an increasingly important place in therapeutic nutrition.

With regard to foods and rations for survival situations and for first-aid and disaster feeding, research and development is urgently needed.

The number of proprietary supplements and therapeutic foods for special diets has increased rapidly during recent years. In examining many of these foods through several years, I have been pleased to note that the manufacturers are giving increasing attention to acceptability. These foods should not only fulfill their nutritional purposes, but also look good, smell good and taste good. This is a promising field for study and development.

Intravenous nutrient solutions of saline, dextrose and amino acids have been extensively used during the past generation. Only within the past ten years have the possibilities of administering fat emulsion been intensively studied (9–11). The fat emulsions are useful in parenteral therapy where the patient either cannot or will

TABLE 2. MORTALITY STATISTICS ON NUTRITIONAL AND METABOLIC DEFICIENCY DISEASES IN THE UNITED STATES FROM 1935 TO 1955

Disease*	1935	1940	1945	1950	1955
Beriberi	7	63	46	36	28
Pellagra	3543	2123†	914†	260	96
Scurvy		26	18	27	13
Rickets		161	93	29	11
Osteomalacia				14	16
Other avitaminoses and nutritional deficiency states:					
Steatorrhea and sprue				60	46
Other vitamin deficiency states				3	7
Malnutrition, unqualified				460	506
Other and multiple defic. states				191	121

Data taken from Vital Statistics—Special Reports and Public Health Reports, Public Health Service, Washington, D. C.

* Data on the nation-wide incidence of nutritional deficiency diseases are not apparently available except for pellagra during 1940, in which 8688 cases and 2123 deaths were reported.

† Does not include deaths fram alcoholic pellagra and other deficiency diseases associated with alcoholism which, in 1940 and 1945 were 68 and 1, respectively.

not take oral nutrients. The emulsifying agents are phosphatides or non-phosphatide surface-active agents. The solutions used so far have contained 10–15% of fat and 4–5% of dextrose. The caloric content is about 1500 Cal/liter. The time of administration is from 3 to 4 hours. Unfortunately, the administration is associated with a 10–30% incidence of fevers of relatively short duration and with other untoward reactions. Unfortunately, too, the addition of salts and amino acids breaks the emulsion. This is an important new field for study and, in the near future, I look forward to the development of new physiological emulsifying agents, or combinations of such, and of purer oils, which will permit the preparation of stable, non-thermogenic, complete nutrient solutions.

3. NEW METHODS IN FOOD TECHNOLOGY

The greatest enterprise of our country is the food industry. Most of the foods we eat today go through many channels and are processed in some manner before they come into the home. The average household, consisting of 3.42 persons, consumes about 70 pounds/week of processed foods, of which about 27 pounds are dairy products and 13 pounds are cereal products (12). The industry's most acute problem is preserving the acceptable qualities—keeping the food from spoiling. To this end, three general processes are widely used, and a fourth one is now under intensive study.

The first of these processes is heat sterilization, which is the basis of the canning industry. It has been established for more than a century, and is the most widely used process at present. There are serious objections to the high temperatures which are employed, the most important of which is the destruction of certain amino acids, resulting in lowered biological value of the proteins. Of course, in a land of plenty such as ours, this is not an important item to worry over, since the national diet contains a plethora of high quality proteins. But, protein quality becomes important in populations subsisting on nutritionally marginal diets.

The second process is refrigeration, which reduces the rate of bacterial spoilage. Food may be kept almost indefinitely at very low freezing temperatures. However, not all foods may be kept simply by freezing. For example, vegetables and some fruits require a brief blanching, or heat treatment, to inactivate enzymes. The freezing process has not been adapted as yet to all foods. The process perhaps brings about the least destruction of vitamins and nutrients of any of the preservation methods. However, frozen foods suffer some change of texture, color, odor and taste. The limitations of this processing method are, however, the dependence upon electricity and the need for refrigerators and continuous refrigeration up to the time of preparation for the table. In spite of this, the process is being rapidly extended and the foods have gained wide public acceptance in a short period of years (13).

The third, and oldest, process is drying. Dried foods have been known since the beginning of civilization. The preserving action is two-fold: first, on chemical reactions, and second, on bac-

terial growth. The greater the degree of desiccation the greater the retardation of chemical and bacterial changes. The process, although simple, brings about changes which influence color, texture and taste. Perhaps the greatest change in treated foods is in the ability to reabsorb water; the greatest difficulties in this respect are experienced with dried meats.

The preparation of dried foods for the table requires considerable training, and the consumer must acquire new standards of acceptability. Perhaps because of this, desiccated foods have not found as wide acceptance in this country as in European countries. However, the best known foods in this category, eggs and fat-free and whole milk solids, are being increasingly used. The technology, particularly the use of vacuum drying, is being intensively studied.

The desiccated foods are ideal for stock-piling, because of their stability and small requirements for storage space. They are readily transported; no refrigeration is required; and they can be stored and used under quite primitive conditions. As noted before, the public has not accepted and acquired a taste for many of the dehydrated foods. However, necessity has tremendous educational force. Under its influence in times of great emergency, this category of foods will undoubtedly become an important item in the diet of the Armed Forces and civilian populations.

The fourth, and newest process, is based upon sterilization or inhibition of growth by ionizing radiations. It is still in the experimental stage, and so far no foods subjected to the process have been placed on the market. The sources of radiations are: *a*) machine-produced, high speed electron beams with variable energies (6 to 24 mev), and *b*) radioactive wastes or spent fuel rods emitting gamma rays or beta particles with either a wide spectrum in beam energies or monoenergetic rays. The effect on the food, however, is essentially the same.

At levels of say, 10,000 to 20,000 rep, insects in grains and the larvae of trichina in pork are controlled. (The term 'rep' means 'roentgen equivalent physical' and is the quantity of ionizing radiation which will result in the absorption of 93 ergs of energy per gram of tissue). At 20,000 to 50,000 rep, sprouting of potatoes and onions is prevented or minimized. These levels of radiations do not produce physical or organoleptic changes in foods. However, at higher levels changes become increasingly apparent (14).

Levels of five million rep are required for complete sterilization of all foods. For most foods, three million rep are sufficient. At this level all foods may show some changes in color and firmness. Thus, vegetables and fruits may have a mushy and slightly 'cooked' appearance. Foods may develop off-odors and flavors. Each food has a critical dosage at which certain effects appear. Thus, at the sterilizing dose of 2.5 million rep, chicken meat may have an unacceptable odor and taste; at two million rep, although not entirely sterile, it may be acceptable (15). However, even if the organoleptic properties of the raw food are affected, the changes may be minimized by care in preparation. For example, in a recent study with human subjects at the U. S. Army Medical Nutrition Laboratory, McGary and co-workers (16) found that 31 of 40 frozen radiation-sterilized foods were as acceptable as unirradiated frozen control foods. This acceptability of 31 out of 40 foods was made possible by the development of enticing recipes of food preparation. Radiation processing, like the other three processes already discussed presents special problems in food preparation for the table. Widespread public acceptance will require not only development of specialized cookery, but also education in new tastes.

High levels of radiation induce changes of chemical and physical characteristics (14). The vitamins are changed or destroyed to about the same extent as by heat sterilization. Thiamine is lost by disruption into the pyrimidine and thiazole moieties; the pyrimidine remains stable, the thiazole is destroyed (17). As in heat sterilization, the proteins may be denatured and the biological value reduced. However, in some instances the change may be greater, in others less. Since the process is new and the products untried, a careful study of the technologic problems and the nutritional adequacy of the foods is needed. This is now being done by the Department of the Army under the guidance of the Quartermaster Corps and the Office of the Surgeon General.

4. CHEMICAL SUBSTANCES ADDED TO FOODS

Food additives are of immense importance in food production and processing. They have been the subject of considerable study and some controversy within recent years. They are of two

kinds: *a*) those added unintentionally or incidentally through the use of pesticides and *b*) those added intentionally in the 'manufacture or formulation of a food or serving a functional purpose' (18). Additives of both kinds are increasing in number and use and, with this, the number and total intake of such foreign substances in natural foods is also increasing. The chemicals of the first group are used in control of insects, rodents and plant diseases during production, manufacture and distribution of food. Although they are toxic, they are essential in our food economy. The great problem in handling these toxic agents is to reduce the concentration, or to eliminate them entirely, after they have exerted their desired action. Education and national legislation have decreased the possibilities of actively toxic quantities in the foods coming to the table.

Of the second group, some 700 of the so-called intentional or functional additives are known. The Food Protection Committee of the Food and Nutrition Board, National Research Council, classifies them under 14 categories: preservatives; anti-oxidants; sequestrants; surfactants; stabilizers and thickeners; bleaching and maturing agents; buffers, acids and alkalies; food colors; non-nutritive sweeteners; nutrient supplements; flavoring agents; miscellaneous, including yeast foods, firming agents, texturizers etc. (18).

The wide range of applications is evident from this listing. Many of the additives like salt, baking soda, vinegar and plant extract flavors have long been known, and add to the palatability and enjoyment of food. Others, like thiamin added to flour, vitamin D to milk, and vitamin A to oleomargarine, increase the nutritional qualities of the processed food.

Considerable public attention and discussion is now being given to these agents. This has been accelerated, perhaps, by publicity of the hearing on several bills before Congress within the past six years for regulation of food additives (19, 20). Of course, toxicity is relative. All substances, even those which are considered 'harmless, like dextrose, salt and amino acids, have a level at which they become toxic. It is important to know the safe limits of use. Although the need for regulation of additives is recognized, the method of control is under debate by industry and governmental regulatory agencies. It is important to control the use within safe limits. Certainly, additives are here to stay because they serve a useful function.

Although quite adequate toxicity data on individual substances have been obtained by industry and governmental agencies, relatively little thought has been given to possible synergistic actions with other additives. As the number and use increases, it is important to consider the possible synergistic action of not one, but many, of these substances, both intentional and unintentional, together in the same diet. We are living in an age when, as never before, man is subjected to chemicals in a wide variety of preparations besides those in foods—all presumably within the 'safe' limits of each chemical *alone* as determined by experiment, and, to some extent, by clinical observation. It is imperative that at intervals long-range experiments be conducted with several animal species on the effects of 'safe' concentrations of the commoner additives together in the same diet.

5. SOME RECENT TRENDS IN NUTRITION

Nutrition is the science of food and its relation to life processes and health. It spans the fields of technology and the biological and medical sciences. Two important recent trends are evident in this science: first, the increasing diversity of research and, second, the broadening of the avenues of dissemination of scientific knowledge. The time-lag is decreasing between the experiment and the interpretation of results to the public. Education is being broadened and is becoming more effective. It is carried into the home, community group, the school lunch room.

As examples of research and its wide publicity I may cite the present studies on fat metabolism. They include experimental and statistical studies on the relation of the caloric intake and the kinds and quantities of fats in the diet to obesity, atherogenesis and cardiac disease. This is still under clinical and laboratory study.

Publication of results of scientific work in the field just mentioned is not only in the professional journals, as heretofore, but also in the daily papers and popular magazines. A surprisingly large number of the articles are written by outstanding researchers, some of them members of this Federation.

In 40 monthly issues of 4 national magazines reaching my home during the past year, I found 22 well-written articles on nutrition with emphasis on weight-control. It is evident to me that

the scientist is overcoming his inhibitions to popular writing. The experimental data are thereby immediately brought to lay attention and they are interpreted by the profession, not by the popular writer. The result has been a public education not only in nutrition and its bearing on health, but also on the methods and problems of the science.

Of course, public education is slow. However, already the layman is becoming conscious of his caloric intake, the kind and quantity of fat (plant or animal), protein quality, and vitamin and mineral content of his food; and the effect is becoming apparent in the food industry. In the livestock industry, the trend is toward production of leaner pork and beef. The leaner breeds of hogs are preferred. The educational efforts have affected not only choice of meats but also the relative preferences for other foods. The quantities of milk and eggs relative to cereals and sugars is changing. With time, I expect a pronounced change in the food habits, which will affect the pattern of food production and technology.

SUMMARY

In summary, I have reviewed some of the advances in several areas of nutrition and technology as follows: nutrients and drugs; therapeutic and special foods; new methods in food technology; chemical additives; and some recent trends in research. Data are presented with reference to production and uses of vitamins, hormones and antibiotics during the years 1940, 1945, 1950 and 1955. Data are also given with respect to incidence of and morbidity from vitamin deficiency diseases. Basic research in nutrition has greatly affected food production and technology. On the other hand, technical advances have contributed to the variety and dietary pattern of man. Advances in nutrition and technology together have improved the public health.

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ANALYSIS OF NATIONAL REGISTER OF SCIENTIFIC AND TECHNICAL PERSONNEL DATA FOR EXPERIMENTAL BIOLOGISTS

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FOR THE PREPARATION and maintenance of the National Register of Scientific and Technical Personnel of the United States, The National Science Foundation has used the services of various professional scientific organizations. In the broad area of biology, the Federation of American Societies for Experimental Biology and the American Institute for Biological Sciences have been the designated collecting agents and as such have circulated questionnaires in their respective areas of biology. In addition to its own membership, the Federation has been responsible for collecting vitae for experimental biologists in fields whose application to medicine and public health is obvious and direct. The data from questionnaires distributed during 1956-1957 by FASEB have now been coded. This report is the first analysis based on information contained in 9,237 returns from experimental biologists at the post-doctoral level. Of 19,640 questionnaires mailed, 14,773 or 75% were returned completed. Of these, 1,833 which fell within the responsibility of other collecting agencies were forwarded to the proper organization. From the total number of respondents, 12,940 in FASEB register, 2,734 were from scientists below the doctoral level and 969 were incomplete for purposes of evaluation. Hence this report deals with an analysis of the data from 9,237 individuals working as biologists and with a doctoral degree. Less than 0.3% of the respondents were women; hence comparative studies of men and women were not made.

The source of contact for the preparation of mailing lists was made by requesting the names of scientific personnel or membership from the type and number of institutions and organizations listed in table 1. Of the 9,237 completed questionnaires evaluated in this report, 41% are members of FASEB.

Since there is an overlap of membership between several collecting agencies a rather arbitrary division of responsibility for collection and codification between such groups as FASEB, AIBS and ACS was determined. As far as the FASEB survey and register is concerned, all scientists making questionnaire returns who are members of FASEB were included no matter what other society membership they might have. However, a scientist belonging to the American Chemical Society, for example, and not a member of FASEB would not be included in this report. This limitation on the completeness of the survey of experimental biologists is most prominent in the case of biochemists and to a less extent for pharmacologists, anatomists and geneticists.

CRITERIA FOR VARIOUS CATEGORIES AND PRESENTATION OF INFORMATION

1. Type of Employer. In table 2 are listed the categories presented in the questionnaire and the code designation of each. For purposes of this report fewer categories are used: 0 is referred to as 'University'; 'Federal Government' includes 2 and 3 and commissioned officers of the U. S. Public Health Service; 'Industry' is 6; 'Non Profit' is 5, and 'Other' includes 1, 4, 7 and 9.

2. Primary Function. Table 3 shows the choices offered in this category. In this report 'Research' is 0; 'Teaching' is 2; 'Administration' includes 5 and 6; Y is listed under 'Clinical Investigation' and all others under 'Other'.

3. Professional Income. Table 4 shows the income levels designated.

4. Professional Field. The categories given in table 5 were used in the original coding as the basis for decision as to the professional field in most instances. However, where there was some question due to overlapping, then the information listed by the scientist of his two highest competencies chosen from a prepared list of specialties was used. In general 'Physiology' is 03 under 25 in table 5; 'Biochemistry' is 09 under 31; 'Nutrition' is 20; 'Microbiology' includes 04, 11, 17, 18, 19, 22 and 27; 'Pathology' includes 14, 21, 23; 'Pharmacology' is 24 while 'General Biology' includes 13, 29, and 'Other'.

TABLE 1. SOURCE OF NAMES FOR QUESTIONNAIRE LIST

170	Medical schools and universities
701	Undergraduate colleges
46	Private industries
72	Non-profit foundations, research hospitals, etc.
36	Federal research organizations, state laboratories
12	Professional scientific societies

TABLE 2. EMPLOYER CHOICES

0. College or university
1. Other educational institution
2. Federal government—civilian employee
3. Military service—active duty
4. State, local or other government (except educational institution)
5. Non-profit organization (other than 0, 1, 2, 3, 4)
6. Industry or business
7. Self-employed
9. Other (specify)

TABLE 3. PRIMARY FUNCTION CHOICES

0. Research
1. Development, design
2. Teaching
3. Consulting
4. Technical writing, editing, patents
5. Management or administration of research and development
6. Management or administration, other than research and development
7. Inspection, analysis, testing, process control
8. Production, construction, installation, operation
9. Technical sales, service, marketing, purchasing
Y. Clinical practice, investigation

TABLE 4. INCOME LEVEL CHOICES

0. Below $2,000	6. $9,000–$9,999
1. $2,000–$3,999	7. $10,000–$11,999
2. $4,000–$5,999	8. $12,000–$15,999
3. $6,000–$6,999	9. $16,000–$19,999
4. $7,000–$7,999	Y. $20,000 and over
5. $8,000–$8,999	

TABLE 5. PROFESSIONAL FIELD CHOICES

03. Anatomist	20. Nutritionist
04. Bacteriologist	21. Oncologist
06. Biophysicist	22. Parasitologist
09. Endocrinologist	23. Pathologist
11. Epidemiologist	24. Pharmacologist
13. Geneticist	25. Physiologist
14. Hematologist	27. Virologist
17. Immunologist	29. Biologist (general)
18. Microbiologist	31. Biochemist
19. Mycologist	Other (specify)

5. Level of Experience. This is based entirely on the number of years elapsed since the respondent obtained his doctoral degree.

6. Distribution of Scientists at Post-Doctoral Level in Experimental Biology; Distribution of All Respondents by Professional Field. The right-hand column of table 6 gives the number and percentage of the 9,237 respondents in each of the seven general professional fields. Here the validity of the relative proportion of the total community of experimental biologists at the post-doctoral level, made up of scientists in any one professional field, is of course limited by the degree of coverage of all those in that field. As pointed out previously, this may be a factor in determining third place for the biochemists behind physiologists and microbiologists. These three fields, however, are much broader and include many more sub-specialties than the others and, therefore, would probably be expected to be larger.

7. Distribution of All Respondents by Type of Doctoral Degree. Thirty-three per cent had an M.D. degree, 58% a Ph.D. and 9% had more than one type of doctoral degree (Ph.D., Sc.D., M.D.). Table 7 gives the distribution of type of degree in each field covered.

8. Distribution of All Respondents by Employer. The totals listed in the bottom line of table 6 indicate that a majority and by far the highest proportion (55%) of the experimental biologists included in the register are employed in universities and colleges, with the federal government second with 17%, and not greatly higher than industry and non-profit institutions other than academic.

9. Distribution of All Respondents by Professional Function. The bottom line of table 8 shows that the majority (52%) of these experimental biologists are engaged with research as their primary function as compared to 23% who are primarily responsible for teaching. Twelve per cent considered themselves as administrators and 9% were engaged in clinical investigation. Since clinical investigation is a research activity this means that a total of 61% were working primarily in research.

10. Distribution by Employer Within Each Professional Field. Table 6 brings out some definite differences in the relative numbers of scientists within any one professional field that are employed by the different categories of employer. The relative numbers in all fields employed by the federal government is about the

TABLE 7. DISTRIBUTION OF EXPERIMENTAL BIOLOGISTS BY TYPE OF DOCTORAL DEGREE

Field	MD		PhD		Mult. Degrees		Total
	%	#	%	#	%	#	
Physiology	42	1129	46	1236	12	310	2675
Biochemistry	10	174	84	1454	6	99	1727
Pharmacology	29	204	56	386	15	107	697
Pathology	81	718	8	67	11	97	882
Nutrition	15	71	81	380	4	16	467
Microbiology	22	509	71	1628	7	172	2309
Other	43	207	52	247	5	26	480
Total	33	3012	58	5398	9	827	9237

same, ranging from 13 to 20%. In universities, there are, also, no marked differences between fields with the range being from 49% for pathologists to 62% for physiologists. In every field, universities employ the highest proportion of scientists. However, in industry there appear to be significant differences with a relatively large proportion of pharmacologists and a small percentage of physiologists and pathologists so employed. Non-profit organizations, on the other hand, employ relatively more of the total biochemists and pathologists than they do of the other professional personnel represented.

TABLE 6. DISTRIBUTION OF EXPERIMENTAL BIOLOGISTS BY FIELD AND TYPE OF EMPLOYER

Field	Fed. Govt.		University		Industry		Non-Profit		Other		Total	
	%	#	%	#	%	#	%	#	%	#	%	#
Physiology	17	466	62	1648	5	120	9	237	7	204	29	2675
Biochemistry	15	257	55	956	10	175	15	260	5	79	19	1727
Pharmacology	13	90	54	377	25	172	4	32	4	26	7	697
Pathology	18	161	49	431	4	32	19	169	10	89	10	882
Nutrition	13	63	63	296	13	59	6	28	5	21	5	467
Microbiology	20	468	50	1152	15	343	8	181	7	165	25	2309
Other	13	61	41	199	10	48	13	63	23	109	5	480
Total	17	1566	55	5059	10	949	10	970	8	693	100	9237

TABLE 8. DISTRIBUTION OF PRIMARY FUNCTION OF EXPERIMENTAL BIOLOGISTS BY PROFESSIONAL FIELD

Field	Research		Teaching		Administration		Clinical Investigation		Other		Total No.
	%	No.	%	No.	%	No.	%	No.	%	No.	
1. Physiology	48	1278	30	794	8	215	12	325	2	63	2675
2. Biochemistry	71	1224	14	247	10	166	2	39	3	51	1727
3. Pharmacology	54	377	23	158	14	95	5	38	4	29	697
4. Pathology	39	340	21	188	11	97	24	215	5	42	882
5. Nutrition	58	269	18	84	16	78	3	13	5	23	467
6. Microbiology	50	1148	24	559	16	369	4	106	6	127	2309
7. General biology	29	139	23	110	13	60	31	149	4	22	480
GRAND TOTAL	52	4775	23	2140	12	1080	9	885	4	357	9237

TABLE 9. DISTRIBUTION OF EXPERIMENTAL BIOLOGISTS BY PRIMARY FUNCTION AND EMPLOYER

Employer	Research		Teaching		Administration		Clinical Investigation		Other		Total No.
	%	#	%	#	%	#	%	#	%	#	
University	49	2461	41	2073	5	267	4	213	1	45	5059
Federal government	63	989	1	20	21	315	9	153	6	89	1566
Private industry	57	541	0	1	29	271	3	30	11	106	949
Non-profit	61	596	2	16	12	114	20	195	5	49	970
Other	27	188	4	30	16	113	43	294	10	68	693
Total	52	4775	23	2140	12	1080	9	885	4	357	9237

TABLE 10. EXPERIMENTAL BIOLOGY SALARY LEVEL BY YEARS OF EXPERIENCE AND FIELD

Years of Exper.	Field	1st Quartile	Median	3rd Quartile	Total No.
0–4	Physiology	$4,734	$6,086	$7,050	524
	Biochemistry	4,654	5,956	6,974	427
	Pharmacology	4,958	6,539	7,801	211
	Pathology	4,216	5,999	7,772	82
	Nutrition	4,974	6,338	7,020	83
	Microbiology	4,834	6,175	7,254	560
	General biology	4,402	5,634	7,134	101
Total		$4,734	$6,117	$7,221	1,988
5–12	Physiology	$6,049	$7,483	$9,175	832
	Biochemistry	6,509	7,519	8,788	577
	Pharmacology	7,065	8,129	10,450	188
	Pathology	6,866	8,637	11,250	257
	Nutrition	6,911	7,969	9,035	134
	Microbiology	6,465	7,693	9,145	747
	General biology	5,922	7,690	9,964	149
Total		$6,413	$7,704	$9,320	2,884
13–27	Physiology	$8,331	$10,682	$14,152	1,014
	Biochemistry	8,323	10,102	12,756	571
	Pharmacology	10,625	12,153	15,952	247
	Pathology	9,942	13,340	16,960	390
	Nutrition	7,270	10,086	14,664	184
	Microbiology	8,382	10,450	13,576	780
	General biology	8,772	12,516	19,568	158
Total		$8,531	$10,888	$14,368	3,344
28+	Physiology	$8,960	$12,243	$16,928	305
	Biochemistry	8,067	10,756	14,000	152
	Pharmacology	9,583	12,140	15,784	51
	Pathology	9,375	13,956	19,664	153
	Nutrition	7,928	10,362	14,500	66
	Microbiology	8,740	10,622	13,920	222
	General biology	11,142	15,999	20,000+	72
Total		$8,782	$11,774	$15,864	1,021
GRAND TOTAL		$6,493	$8,405	$11,588	9,237

TABLE 11. EXPERIMENTAL BIOLOGY SALARY LEVEL BY YEARS OF EXPERIENCE AND EMPLOYER

Years of Exper.	Employer	1st Quartile	Median	3rd Quartile	Total No.
0–4	Federal government	$5,454	$6,706	$7,622	391
	University	4,468	5,532	6,543	1,087
	Industry	7,174	7,776	7,625	231
	Non-profit	4,286	5,818	6,967	202
	Others	4,630	$6,194	$7,593	77
Total		$4,732	$6,118	$7,223	1,988
5–12	Federal government	$7,161	$8,303	$9,848	539
	University	6,120	7,164	8,410	1,566
	Industry	8,507	9,866	11,912	288
	Non-profit	6,090	7,593	9,420	322
	Others	6,539	8,586	12,404	169
Total		$6,415	$7,705	$9,338	2,884
13–27	Federal government	$9,051	$10,788	$12,808	530
	University	7,980	9,841	13,004	1,828
	Industry	10,796	13,620	18,044	366
	Non-profit	9,310	12,740	16,740	319
	Others	9,965	14,352	20,000+	301
Total		$8,529	$10,888	$14,368	3,344
28+	Federal government	$10,250	$12,016	$12,228	106
	University	8,311	10,796	14,464	578
	Industry	11,666	18,856	20,000+	64
	Non-profit	9,175	13,768	20,000+	127
	Others	8,892	14,300	20,000+	146
Total		$8,744	$10,176	$15,864	1,021
GRAND TOTAL		$6,493	$8,405	$11,588	9,237

11. Distribution of Function Within Each Professional Field. Details of table 8 indicate that in individual fields the relative proportion of scientists engaged in the designated functions varies and does not necessarily parallel the overall functional distribution. There is obviously more than the average proportion of biochemists engaged in research and fewer primarily in teaching. General biologists and pathologists, on the other hand, have a lower than average proportion in research. There does not appear to be any definite difference in the relative number in any field engaged in administration but the physiologists, pathologists and general biologists have greater percentages than the average in clinical investigation. This high percentage of general biologists in clinical investigation requires some interpretation. It probably reflects the fact that a number of M.D.'s doing clinical investigation as a primary function could not be readily classified in any other professional field and were, therefore, included under general biology.

12. Distribution of Functions by Type of Employer. In table 9 are shown some comparisons of relative numbers of scientists engaged in the designated functions with the different categories of employer. Universities have a lower proportion engaged primarily in research yet more are primarily in research than primarily in teaching. The

TABLE 12. EXPERIMENTAL BIOLOGY SALARY LEVEL BY EMPLOYER AND PRIMARY FUNCTION

Employer	Function	1st Quartile	Median	3rd Quartile	Total No.
University	Research	$5,660	$7,219	$9,232	2,461
	Teaching	6,304	7,912	10,530	2,073
	Administration	9,940	12,700	15,916	267
	Clinical invest.	5,424	9,708	16,124	213
	Other	6,208	8,500	13,376	45
Total		$6,093	$7,728	$10,436	5,059
Federal Government	Research	$6,700	$7,978	$9,837	989
	Teaching	7,500	12,000	13,140	20
	Administration	9,465	11,178	13,404	315
	Clinical invest.	7,260	8,931	12,620	153
	Other	7,019	8,730	11,146	89
Total		$7,087	$8,650	$11,104	1,566
Industry	Research	$7,859	$9,026	$11,610	541
	Teaching	12,000	Insignificant Number		1
	Administration	11,214	14,620	20,000+	271
	Clinical invest.	9,375	13,500	17,664	30
	Other	7,531	9,600	13,156	106
Total		$8,265	$10,480	$14,448	949
Non-profit	Research	$5,824	$7,477	$10,210	596
	Teaching	8,000	14,664	19,000	16
	Administration	9,083	12,800	17,284	114
	Clinical invest.	6,527	12,631	20,000+	195
	Other	7,541	9,700	14,872	49
Total		$6,219	$8,569	$13,320	970
Other	Research	$6,300	$8,437	$11,832	188
	Teaching	6,250	8,500	15,332	30
	Administration	8,446	10,882	14,676	113
	Clinical invest.	11,226	17,100	20,000+	294
	Other	5,600	8,500	14,000	68
Total		$7,588	$11,672	$18,040	693
GRAND TOTAL		$6,493	$8,405	$11,588	9,237

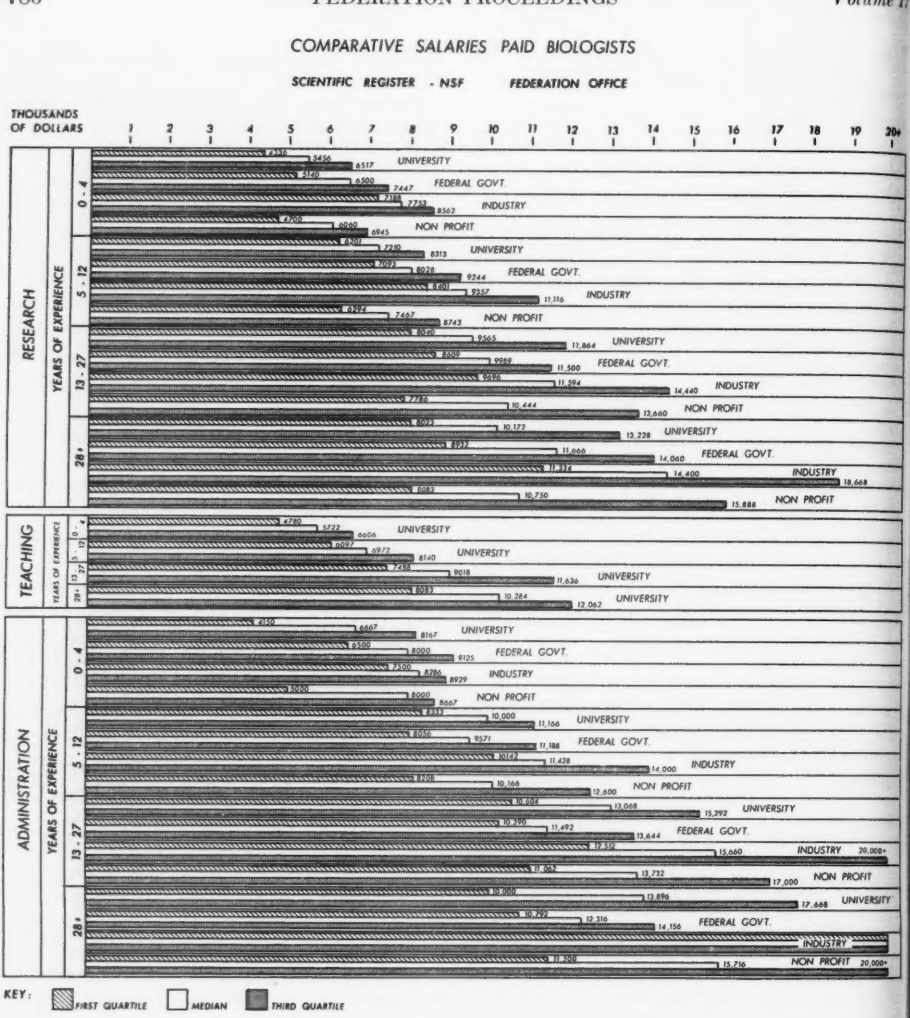
mall percentage who are engaged in teaching in ll types of employment other than universities complemented by the much higher proportion administration. Whereas government and dustry use 21 and 29% in administration, the niversities have only 5%. Non-profit organizaons which include hospitals have a high proporon in clinical investigation. The very high gure for clinical investigation under 'Other' is ue to the inclusion of a number of M.D.'s who e self-employed.

13. Salary Range at Post-Doctoral Level for Experimental Biologists. All data on salary ranges are presented by quartiles since this represents a better distribution basis for comparison than percentage figures in each salary bracket. Evaluation of salary ranges is obviously more meaningful if only those individuals of equal experience are compared. Since from information available in this survey, experience can be estimated best by the number of years since the doctoral degree was awarded, salary tabulations in tables 10 and 11 are made on this basis. However, in table 12 this was not possible within the framework of the two variables, namely employer and function and, therefore, salary ranges in this table represent all those in the indicated categories unrelated to years of experience.

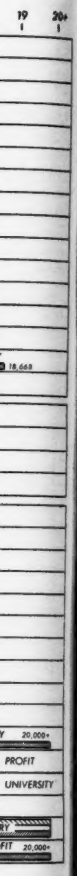
Table 10 compares salary ranges by field for four levels of 'experience'. Although differences appear to be small it can be seen that once one gets beyond five years of experience, there is a tendency for pharmacology, pathology and general biology to be about one salary bracket higher than the other fields in most quartiles. At this point some explanation should be made for the field of 'General Biology'. Of the 480 respondents included in this field, 174 are those with the M.D. degree only, principally engaged in clinical investigation, many of whom are also in the practice of medicine. The remaining group of 306 is composed of 80 geneticists, 79 zoologists, 38 botanists, 69 physiological psychologists, 22 biophysicists and 18 general scientists.

Salary ranges at each level of experience are compared in table 11 between various employers. In practically all 'experience' categories university salaries are lower than those of any other type of employer and industry is higher. Federal government salaries in general are between the two extremes. Non-profit non-academic institutions tend to be relatively low and comparable to universities for those with fewer years of experience but beyond 12 years' experience tend to be higher than federal government. Interesting comparisons are possible by determining what the lower salary limit is for one half or three fourths of all those in any group. For instance, of those with 13 to 27 years experience, one half in federal government earn over $10,000; in universities over $9,000; but in industry and non-profit groups over $12,000.

Table 12 attempts to compare salary ranges for all those under any one employer according to



their primary function. Since this table is not broken down by years of experience, the comparisons are more general and in the case of 'Administration' obviously are biased by the fact that scientists in administrative positions tend to be those with more years of experience and for this reason would command higher salaries. However, there appear to be certain general trends. In practically all quartiles for every type of employer those in research fall into the lowest salary bracket. In the case of universities, the only employer with significant numbers whose primary function is teaching, teaching salaries are higher than research, but for all employers top salary levels are found for those engaged in administration and clinical investigation.



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